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Address for literary contributions Dr J. N. Lunn, The Editor, *Anaesthesia*, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, UK [telephone Cardiff (0222) 763601; Ansafone available].

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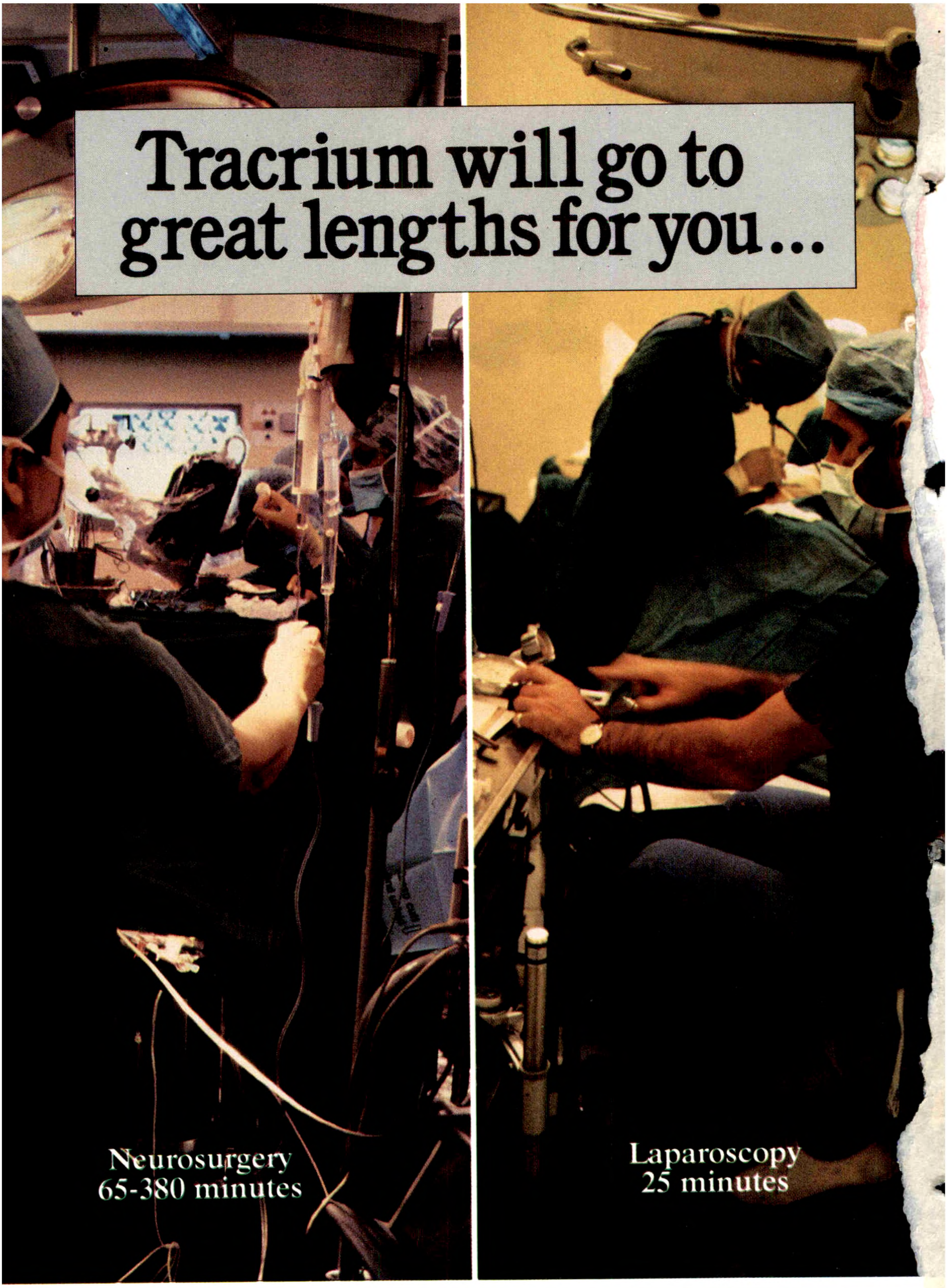

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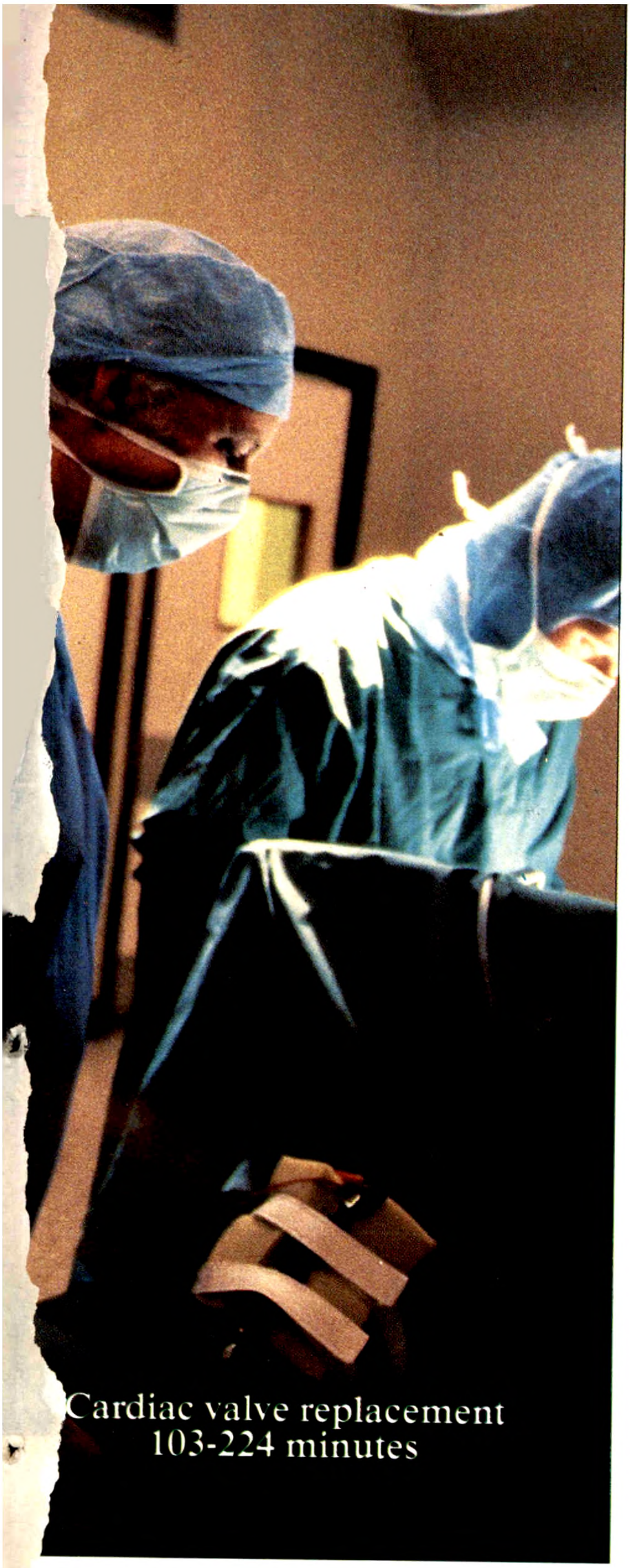

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Anaesthesia, 1987, Volume 42, pages 467–469

Editorial

Bursting the alveolar bubble*

In attempting to rationalise the course of pulmonary oedema or any lung disease, it is useful to have a realistic mechanical model of the alveolus. Hitherto the alveolus has been generally assumed to be lined with a continuous layer of liquid as though it were the inside of a bubble whose collapsing pressure (ΔP) can be very conveniently related to the surface tension (γ) and radius of curvature (r) by the Laplace equation $\Delta P = 2\gamma/r$. This bubble model undoubtedly applies in many pathological states where alveolar flooding is common but its use to describe the normal physiological state is open to debate. Foam expressed from a lung is stable because the air inside each bubble is compressed to a different pressure given by ΔP in the equation above. However, for a number of *open* bubbles of varying size, there can be no common value of ΔP. When interconnected, smaller bubbles shrink while the larger ones grow as the ever increasing difference in ΔP drives air from one bubble to another, causing collapse to be self-accelerating.

The bubble model has been defended on the basis of experiments which show that, upon expanding a monolayer of the surfactant generally assumed to coat the liquid lining of the alveolus, the surface tension (γ) increases more rapidly than the corresponding value of r in the Laplace equation such that all alveoli attain the same value of ΔP. This standard explanation[1] for alveolar stability is fine for one breath but involves differences in surface tension between adjacent alveoli which are difficult to conceive over time or between different points on the same liquid layer. Protein facilitates the rapid exchange of surfactant with the hypophase to attain the unique value known as the equilibrium surface tension, while it is difficult to envisage a liquid lining which is continuous within each alveolus without that continuity extending to its neighbours *via* terminal airways or the pores of Kohn.

Such arguments that emphasise the inherent instability of interconnected bubbles, led to the concept of interdependence[2] whereby adjacent alveoli could stabilise each other by virtue of their back-to-back configuration. This undoubtedly holds for larger lung units but the fact that atelectasis can occur at the micro-level returns us to the concept of alveoli as *independent* rather than interdependent units.

According to the bubble model, the role of surfactant is restricted entirely to the liquid–air interface where it reduces the surface tension to near zero in order to decrease inflation pressure (ΔP in the equation) and maintain homeostasis. ΔP is also the negative hydrostatic pressure of the aqueous hypophase which tends to suck more liquid into the air space and interstitium. It seems a major omission that conventional theory, which postulates a continuous liquid layer, does not offer a mechanism for maintaining its thickness. Validation of the bubble model is based largely upon near-zero readings of surface tension obtained on a Wilhelmy balance monitoring a monolayer of lung surfactant cycled over a wide (5:1) area change on the pool of a Langmuir trough, as used by physicists to study the very interesting phase changes which film compression provokes. However, if the moving barrier is intended to simulate respiratory movement, then area changes cannot exceed 25% (5:4 rather than 5:1) on the basis of morphological studies, when surface tension does not fall below the equilibrium value[3] of 25 mN/m. There is also the serious error incurred in most physiological studies which use the Wilhelmy method yet ignore the large (50–60°) contact angle which surfactant can introduce by its direct adsorption onto the plate, thus giving falsely low values.[3]

The use of equilibrium values for γ in the Laplace equation now gives a collapsing pressure (ΔP)

* This Editorial is loosely based on a lecture at the Annual Scientific Meeting of the Association of Anaesthetists of Great Britain and Ireland in September 1986.

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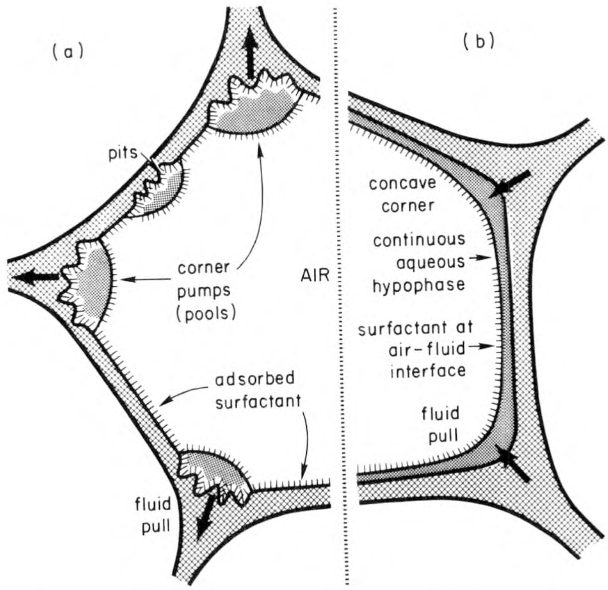

Fig. 1. (a) The water-repellent model of the alveolus with fluid confined to pools and pits, as seen in electron microscopy.[5] From these the fluid can tension the dry patches of the wall by pulling in excess epithelial membrane as pleats. The gas transfer surface is kept essentially dry by water repellency induced by a monolayer of surfactant directly adsorbed onto the epithelial surface. The pools can assume a convex profile to act as corner pumps[4] for returning fluid to the interstitium. If flooding continues, the pools will link up to form the bubble model (b) but as a *pathological* and not the normal physiological state.

which is too large (3.3 kPa) for alveolar inflation or homeostasis in such small mammals as the shrew or bat (r = 14 μm) or in the septal corners of human alveoli. These adverse mechanical aspects of the bubble model and the whole problem of its inherent instability can be avoided if there is no continuous liquid lining, i.e. no bubble in the first place. This has led[4] to the water-repellent model shown in Fig. 1(a), which is more consistent with morphological studies which show liquid confined to pools and pits[5] in which the epithelium is pleated, as in soaking wrinkles. The fluid-free areas are also the gas exchange surfaces over which it makes no sense to add the diffusional resistance of a liquid layer. Fluid is retained from bursting onto those 'dry' areas by water repellency induced by surfactant whose direct adsorption onto epithelium has been demonstrated by Ueda *et al.*[6] The industrial cousins of pulmonary surfactant have been widely used for several decades as water repellents in the textile industry, where chemists talk in terms of the breathability of a fabric. By this they mean that gases and water vapour can pass freely in either direction but liquid water cannot penetrate, the ideal properties for alveolar epithelium. Similarly, the major component of lung surfactant (dipalmitoyl lecithin) is an effective water repellent capable of imparting water penetration pressures well in excess of normal pulmonary arterial pressure.[4] Water repellency can also explain the characteristic onset of alveolar flooding described[7] as a fairly sudden burst through, that is, a flow/no flow phenomenon in which osmotic calculations do not seem to apply to epithelium to the extent that the Starling hypothesis applies to endothelium. Maybe the addage that 'water goes wherever protein goes'[7] should be turned around to read that 'protein goes wherever water goes'.

Separated by dry areas, the pools and pits can now have an edge and a profile which is *convex* with respect to air as opposed to *concave* by the bubble model. Thus they can still tension the 'dry' walls[3] but curvature will now serve to return fluid to the interstitium with a pressure which will be self-regulating since, as more fluid is resolved, the curvature will be reduced (r increased) and the restoring pressure (ΔP) will decrease. Thus, an equilibrium surface tension well above zero is now an *advantage*,

rather than a disadvantage, in maintaining homeostasis. Moreover, departure from the concave profile of the bubble model avoids the need to postulate a negative interstitial pressure of 9 mmHg or so which makes it difficult to conceive how lymph could flow or how such a flaccid structure as the alveolar septum could withstand such crushing pressures.

Much other evidence for a dry *versus* a wet alveolus has been discussed elsewhere,[3] but one particular criticism of the new alveolar model has raised the issue of how water repellency can be restored after flooding, just as the inside of a tent in the rain needs to be kept dry. One possible mechanism is the disjoining pressure which is most commonly observed when removing water from a Teflon-lined frying pan. Below a thickness of 1–1.5 mm the liquid layer spontaneously ruptures to expose dry patches, and pulmonary surfactant adsorbed to glass ruptures a film 900 μm in thickness,[8] that is, six times thicker than the alveolar radius of the human.

Hence surfactant should be considered not simply as a detergent but for the water repellency it can impart when directly adsorbed to alveolar epithelium.

Department of Physiology,
University of New England,
Armidale, New South Wales 2351,
Australia

B.A. Hills

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Anaesthesia, 1987, Volume 42, pages 470–475

Prolonged and biphasic respiratory depression following epidural buprenorphine

F. MOLKE JENSEN, N.-H. JENSEN, I. K. HOLK AND M. RAVNBORG

Summary

Ventilatory sensitivity to carbon dioxide was measured in six healthy volunteers before, and at various times up to 20 hours after, administration of epidural buprenorphine 0.15 mg with a modified Read rebreathing technique. The carbon dioxide response curves were depressed in a time-dependent, prolonged and biphasic manner. Significant depression was seen in the intercept values at an end tidal carbon dioxide of 7.2 kPa, for mouth occlusion pressure ($p < 0.01$), tidal volume ($p < 0.05$) and minute ventilation ($p < 0.05$). A significant reduction of slope was obtained only for minute ventilation. Linear regression of respiratory rate changes during carbon dioxide stimulation, did not reach statistical significance. In conclusion, these data indicate that epidural buprenorphine, despite a high lipid solubility, causes respiratory depression to the same extent as epidural morphine. Surveillance of patients who receive epidural buprenorphine for postoperative pain relief is necessary.

Key words

Anaesthetic techniques; epidural.
Analgesics; buprenorphine.

The use of intrathecal [1] and epidural [2] morphine for postoperative pain relief is now widely accepted and is restricted only by the risk of delayed respiratory depression. Several reports have been published that concern this severe adverse reaction,[3] and prolonged [4] and biphasic respiratory depression have been shown.[5,6] Rostral spread of morphine within the cerebrospinal fluid has been suggested to be responsible for the delayed respiratory depression [7] and evidence in support of this theory has been published.[8–10]

The fraction of narcotic which enters the cerebrospinal fluid following epidural administration, depends on physicochemical characteristics such as the pK_a, lipid solubility and pH of the intercellular fluid. Once the narcotic reaches the cerebrospinal fluid, penetration from the water phase of the cerebrospinal fluid to the lipid phase of the underlying neuraxis occurs at a speed that is determined by the relative lipid solubility of the drug. Drugs that are poorly lipid soluble, such as morphine, will tend to linger in the water phase of the cerebrospinal fluid, to be carried rostrally by the existing cerebrospinal fluid bulk flow.[8]

The ideal opioid for epidural use would possess a high lipid solubility, high affinity for the opiate receptor and a long duration of action. Buprenorphine, which is a partial opiate agonist, fulfils these criteria.[11] The long duration of action despite the high lipid solubility, is

F. Molke Jensen, MD, N.-H. Jensen, MD, I.K. Holk, MD, M. Ravnborg, MD, Department of Anaesthesia and Intensive Care, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark.

Requests for reprints should be addressed to: F. Molke Jensen, Hørvænget 11, DK-4681 Herfølge, Denmark.

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due to a slow dissociation from the opiate receptor complex.[12] Several reports of pain relief following epidural buprenorphine have been published[13–19] but no clinical signs of delayed respiratory depression have been mentioned. The purpose of this study was to evaluate the degree and time course of respiratory depression after epidural buprenorphine.

Methods

Six healthy male volunteers, aged 29–36 years, were included in the study, which was approved by the regional ethical committee. Each subject was studied for a 24-hour period beginning at 09:00, after 9 hours fasting and abstention from tobacco and caffeine-containing liquids. Measurements were made with the subjects in a supine position in a quiet environment. An epidural catheter was inserted at L_3–L_4, and 8 ml of 1% plain lignocaine were injected in order to validate catheter placement. The epidural catheter remained in place throughout the study. Preservative-free buprenorphine 0.3 mg was diluted in 19 ml of isotonic saline to a total volume of 20 ml. Ten millitres of this solution (0.15 mg buprenorphine) were injected through the catheter, which was flushed with 2 ml of saline.

The ventilatory response to carbon dioxide was determined with a modification of the Read rebreathing technique.[20] Subjects breathed a mixture of 6% carbon dioxide, 50% oxygen and 44% nitrogen in a closed system that contained 10 litres of the mixture, and the inspired carbon dioxide concentration was allowed to increase to 9–10%. The respired gas was sampled continuously at the lips at a rate of 0.5 litres/minute, and the carbon dioxide concentration measured with an infrared analyser (Capnograph, Godart). The analyser was calibrated before each carbon dioxide stimulation with two gas mixtures (0 and 6% carbon dioxide). The carbon dioxide concentration was recorded simultaneously on a paper recorder (Godart). Occlusion pressure, the negative pressure generated during inspiration against a closed inspiratory valve in the first 0.1 second ($P_{0.1}$), was measured using a modified method as described by Whitelaw *et al.*[21] This modification allowed several measurements to be made during each carbon dioxide stimulation without the subjects' knowledge. The value of $P_{0.1}$ was recorded simultaneously on the same paper recorder as the carbon dioxide concentration.

Approximately 15 $P_{0.1}$ recordings were made during each session. The tidal volume (V_T) of the inspiration in which $P_{0.1}$ was measured, was determined using a fluidistor (Aga US 800). Respiratory rate was measured from the $P_{0.1}$ tracing, and minute ventilation ($\dot{V}_E$) calculated as the multiplication of respiratory rate and tidal volume.

For each carbon dioxide response curve, least-squares linear regression parameters were calculated for the values of end tidal carbon dioxide pressure ($P_{E'CO_2}$) *versus* the natural logarithm of $P_{0.1}$, and $\dot{V}_E$, V_T and respiratory rate, yielding correlation coefficients (r), slope values (S) and intercepts (i) for each variable. In order to compare statistically the positions of the response curves, intercept values were calculated at a $P_{E'CO_2}$ of 7.2 kPa. Thus, curve position was defined as $P_{0.1\,(7.2)}$, $\dot{V}_{E\,(7.2)}$, $V_{T\,(7.2)}$ and respiratory rate $f_{\,(7.2)}$. A control carbon dioxide response curve was obtained preceding the injection of buprenorphine 0.15 mg through the epidural catheter and then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 20 hours.

In order to perform statistical evaluation of the respiratory parameters, data for variation with time were analysed using a Friedman test. A Wilcoxon rank-sum test was used when comparing data to control values. The level required for significance was chosen as $p < 0.05$.

The subjects were monitored during the observation period with a continuous ECG tracing and transcutaneous P_{CO_2} electrode including an alarm unit.

Results

A high degree of correlation was obtained for the individual regression curves of $P_{0.1}$, $\dot{V}_E$ and V_T with $P_{E'CO_2}$ during the rebreathing test. The correlation coefficients (r) ranged from 0.68 to 0.99. The correlation coefficients for respiratory rate were too small on several occasions to reach significance. For this reason no further computations were made using respiratory rate as an indication of ventilatory sensitivity to carbon dioxide.

The overall statistical evaluation of the data is shown in Table 1. Epidural buprenorphine

Table 1. Statistical evaluation of respiratory measurements following epidural buprenorphine 0.15 mg. Comparisons are with control values at time 0 (Wilcoxon rank-sum test). Time course indicates evaluation of data from the six subjects at all times using Friedman two-way analysis of variance.

Time after epidural buprenorphine (hours)	S $P_{0.1}$	$P_{0.1\ (7.2)}$	S V_T	$V_{T\ (7.2)}$	S $\dot{V}_E$	$\dot{V}_{E\ (7.2)}$
0.5	NS	<0.05	NS	NS	NS	NS
1	NS	<0.05	NS	NS	NS	<0.05
2	NS	<0.05	NS	<0.05	NS	<0.05
3	NS	<0.05	NS	NS	<0.05	NS
4	NS	<0.05	NS	<0.05	<0.05	<0.05
6	NS	NS	NS	NS	NS	NS
8	NS	<0.05	NS	NS	NS	<0.05
10	NS	NS	NS	NS	NS	NS
12	NS	NS	NS	NS	NS	NS
20	NS	NS	NS	NS	NS	NS
Time course	NS	<0.01	NS	<0.05	<0.05	<0.05

S, Slope of regression line; 7.2, intercept value at end tidal carbon dioxide of 7.2 kPa; $P_{0.1}$, mouth occlusion pressure in the first 0.1 second; V_T, tidal volume; $\dot{V}_E$, minute volume.

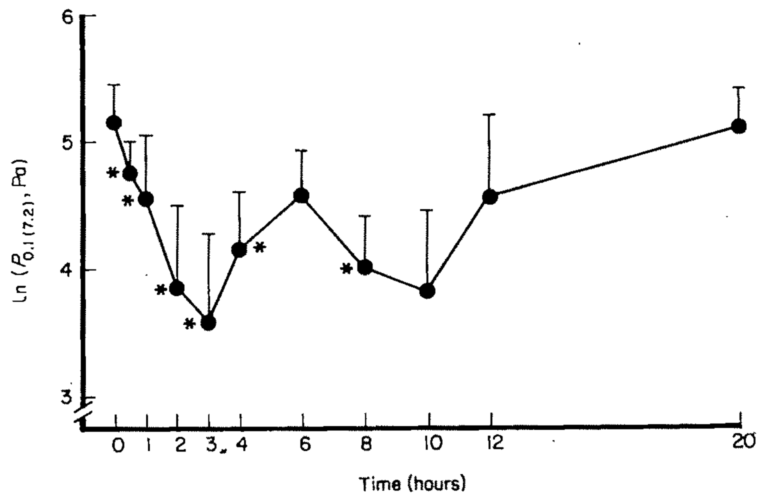

Fig. 1. Position of the mouth occlusion pressure ($P_{0.1}$) response to carbon dioxide (ln, natural logarithm). Calculated P_{CO_2} = 7.2 kPa ($P_{0.1\ (7.2)}$) before (time 0) and at various times after administration of epidural buprenorphine 0.15 mg. Mean (SEM) for the six volunteers. All values are significant compared to time 0 ($p < 0.01$, Friedman test). Asterisks indicate a significant difference compared to time 0 ($p < 0.05$, Wilcoxon rank-sum test).

predominantly reduced the intercept values, whereas a significant reduction in the slope of the carbon dioxide response curve was only achieved for minute volume. This indicates that epidural buprenorphine affects ventilatory sensitivity to carbon dioxide through a displacement of the carbon dioxide response curve to the right. The time-dependent, biphasic reductions in $P_{0.1\ (7.2)}$, $\dot{V}_{E\ (7.2)}$, $V_{T\ (7.2)}$ and minute volume slope are shown in Figs 1–4; the second phase occurs after 8–10 hours. Approximately normal values were obtained at 12 and 20 hours after drug administration. No clinical signs of respiratory depression were observed.

Three subjects (50%) experienced pruritus localised in the groin, which began 2 hours after drug administration and persisted for 4–6 hours. Three subjects (50%) experienced both sedation and nausea, which started during the second hour and lasted 12 hours. Normal ECG recordings and transcutaneous P_{CO_2} values were obtained during the observation period.

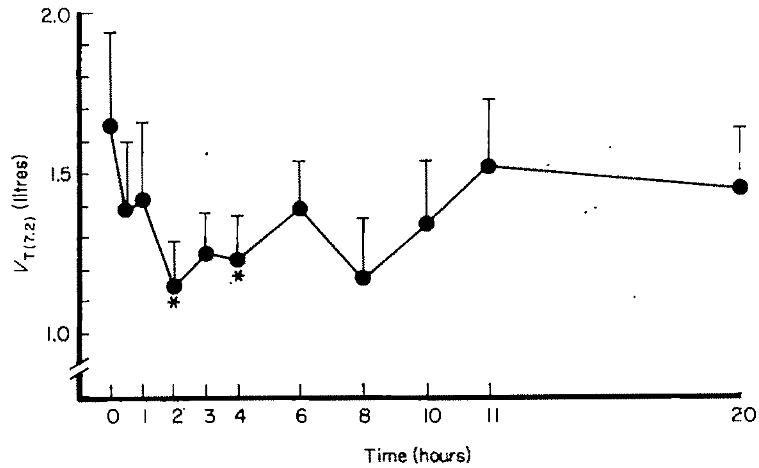

Fig. 2. Position of tidal volume (V_T) response to carbon dioxide. Calculated $P\text{CO}_2$ = 7.2 kPE ($V_{T\ (7.2)}$) before (time 0) and at various times after epidural buprenorphine 0.15 mg. Mean (SEM) for the six volunteers. All values are significant compared to time 0 ($p < 0.05$, Friedman test). Asterisks indicate a significant difference compared to time 0 ($p < 0.05$, Wilcoxon rank-sum test).

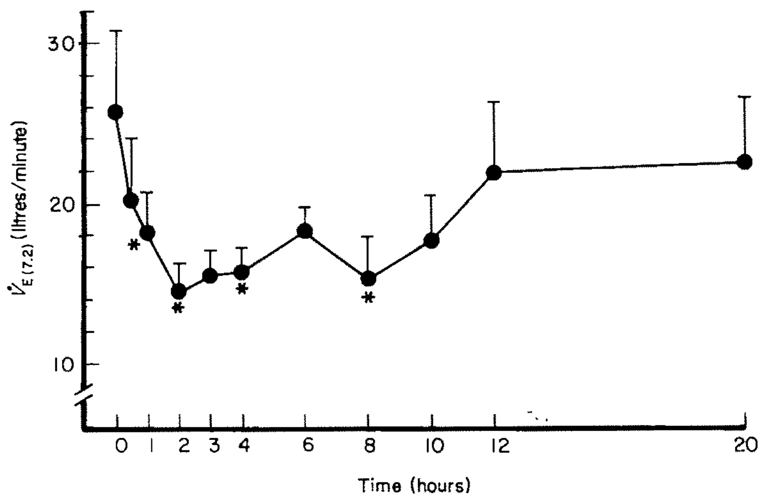

Fig. 3. Position of ventilatory response ($\dot{V}_E$) to carbon dioxide. Calculated $P\text{CO}_2$ = 7.2 kPa ($\dot{V}_{E\ (7.2)}$) before (time 0) and at various times after epidural buprenorphine 0.15 mg. Mean (SEM) for the six volunteers. All values are significant compared to time 0 ($p < 0.05$, Friedman test). Asterisks indicate a significant difference compared to time 0 ($p < 0.05$, Wilcoxon rank-sum test).

Discussion

Healthy volunteers were studied so as to ensure reproducibility and to eliminate the influence of pain on the measurements of respiratory variables.[22] In order to detect any depression of ventilation by epidural buprenorphine, carbon dioxide stimulation of the respiratory centre was chosen and the response determined by measurement of several variables. The results obtained show that epidural buprenorphine produces a prolonged, biphasic depression of the carbon dioxide response, in which the second maximum occurs between 8 and 10 hours after injection. These results are comparable to those obtained after epidural morphine.[4-6]

It was surprising to find a biphasic respiratory depression following epidural buprenorphine, as we expected to find an early depression due to vascular uptake from the epidural space and no late depression because of the high lipid solu-

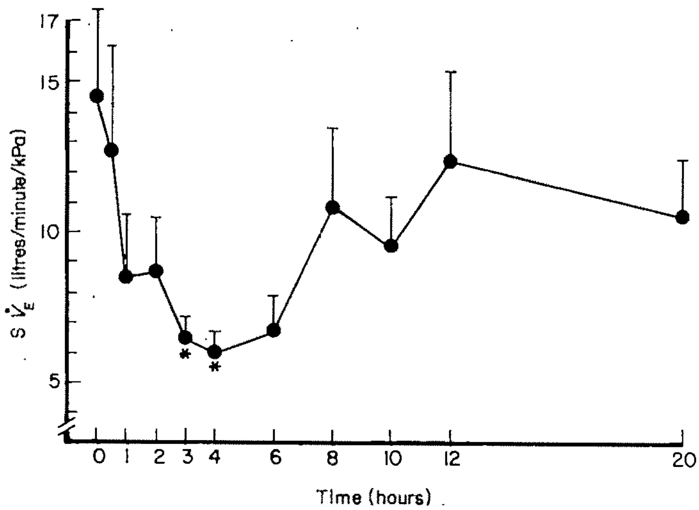

Fig. 4. Slopes of the ventilatory response ($\dot{V}_E$) to carbon dioxide before (time 0) and at various times after epidural buprenorphine 0.15 mg. Mean (SEM) for the six volunteers. All values are significant compared to time 0 ($p < 0.05$, Friedman test). Asterisks indicate a significant difference compared to time 0 ($p < 0.05$, Wilcoxon rank-sum test).

bility of the drug. The reason for this time course may be the long duration of action of buprenorphine; vascular uptake produces early depression and maintains some effect throughout the 8 hours, where a pronounced depression is obtained due to an additive effect of small amounts of buprenorphine carried rostrally by the cerebrospinal fluid. This reasoning is, of course, speculative, and only further studies can reveal the true nature of respiratory depression following epidural buprenorphine.

However, the clinical relevance of these observations in patients who receive epidural buprenorphine is not entirely clear, since no previous reports of respiratory depression have been published. Epidural buprenorphine produced marked depression of the response to carbon dioxide in our subjects, but no clinical signs of respiratory depression were observed. The incidence of late respiratory depression following epidural morphine is low and the aetiology, multifactorial.[23] It has been reported to occur only in the postoperative period and concomitant administration of parenteral opioids or sedatives seems to be an important factor for its clinical manifestation. Other risk factors include high doses, thoracic administration, advanced age and impaired respiratory function.[23] One or several of these predisposing factors were avoided in the earlier studies[13–19] and the risk of clinical respiratory depression was thereby minimised. Animal experiments have shown that opioid depression of medullary nuclei results in reduction of tidal volume and carbon dioxide sensitivity,[24] whereas depression of pontine nuclei results in reduction of respiratory rate that terminates in apnoea. The location of the interaction of epidural opioids with ventilation is believed to be the ventral medullary chemoreceptor zones and the superficial nuclei on the floor of the fourth ventricle.[4] Considering these results, respiratory rate is an unreliable index of impaired respiratory sensitivity to carbon dioxide, and concomitant administration of epidural opioids and general central depressants is potentially dangerous.

In conclusion, our results indicate that epidural buprenorphine exerts a respiratory depression similar to that of epidural morphine, despite its high lipid solubility. The depression is prolonged and biphasic. On the basis of these findings, we recommend that patients who receive epidural buprenorphine for postoperative pain relief, should be under surveillance for at least 12 hours and concomitant administration of respiratory depressants should be avoided.

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Contamination control in long-term ventilation

A clinical study using a heat- and moisture-exchanging filter

J. GALLAGHER, J. E. M. STRANGEWAYS AND J. ALLT-GRAHAM

Summary

Twenty-eight patients who required periods of mechanical ventilation for up to 22 days in the intensive therapy unit were studied to evaluate the clinical use of the Pall Ultipor Breathing System Filter (BB50T) as a heat- and moisture-exchanging bacterial filter. Results in this group of patients showed that there was no longer any need to sterilise breathing systems or decontaminate ventilators if these filters were used. They also performed satisfactorily as a heat and moisture exchanger in patients in need of long-term ventilation, and their use appears to offer substantial advantages as regards cost, ease of use and patient safety.

Key words

Equipment; heat and moisture exchanger, bacterial filter, ventilator.
Intensive care.

The debate over the decontamination of ventilators is not new.[1] A recent survey by the Department of Anaesthesia at St. James' Hospital has shown that, despite the introduction and widespread use of bacterial filters, there is still no clear policy concerning the cleaning of ventilators. The availability of in-line condensing humidifiers (heat and moisture exchangers) made of modern materials has re-opened the debate about humidification of inspired gases in ventilated patients.

The Pall Ultipor Heat and Moisture Exchanging Filter (BB50T) consists of a pleated membrane composed of resin-bonded ceramic fibres; this provides an area of 10 sq. m for heat and moisture exchange with a mechanical dead-space of 63 ml. It is an effective heat and moisture exchanger (HME) even with dry gases under laboratory conditions[2,3] and the use of HMEs as sole humidifiers in artificially ventilated patients is gaining clinical support.[4,5] Buckley,[6] however, reported increased resistance to airflow in some patients but it appeared that incorrect positioning of the HME was at least partly responsible. The manufacturers claim that the HME acts as an effective bacterial filter which will prevent the passage of 99.999% of bacteria for up to 24 hours under varying conditions of humidity and airflow.[7] Theoretically, therefore, it should not be necessary to decontaminate ventilators between patients if such an HME has been used as specified.

This clinical study investigated the effectiveness of Pall HMEs as bacterial filters when they were used as sole humidifiers in patients who were receiving artificial ventilation in the

J. Gallagher, FFARCS, Locum Senior Registrar, J.E.M. Strangeways, FRC Path., Consultant Microbiologist, J. Allt-Graham, BSc, FFARACS, Consultant Anaesthetist, St. James' Hospital, Sarsfeld Road, London SW12 8HW.

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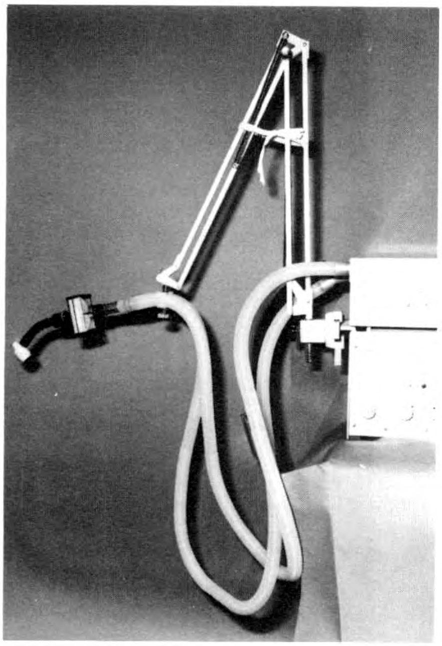

Fig. 1. Breathing system showing position of HME filter.

ITU. In view of Buckley's findings,[6] measurements of resistance to airflow were made after 24 hours of use.

Method

Patients who required mechanical ventilation in the intensive therapy unit (ITU), for a period greater than 12 hours, entered the study during a 5-month period (January–June 1985). The entire complement of intensive care ventilators was used; this consists of one Engström Erica, three Siemens Servo 900B and three Cape 2000. All the ventilators were disinfected and their autoclavable parts sterilised before the study commenced; subsequently no further decontamination was to be carried out unless contamination was suspected or servicing undertaken. All patients who entered the trial received clinically clean, disposable breathing systems (Intersurgical Limited) and filters fitted in accordance with Fig. 1.

The date and time of entry were noted on the patient's record. Breathing systems remained with the patient for the entire period of ventilation (single-patient use). Filters were changed every 24 hours unless a build-up of secretions or exudates was seen within the filter or an unexplained rise in airway pressure was observed. In these instances, the filter was replaced as described below and kept for analysis. Breathing systems were not disconnected during use except for filter changing, as described below, and incorporation of an oxygen analyser into the inspiratory limb. All other routine ventilator care remained unchanged. The filter was changed at 14:00 hours daily with gloved hands according to a set procedure; the new filter was attached to the Y-piece prior to removal of the used filter from the catheter mount. The used filter was capped at both ends and its resistance measured by the pressure drop across the filter, using a water manometer calibrated in cm H_2O with a fixed airflow of 50 litres/minute. Any filter with resistance (R) greater than 0.18 kPa/litre/second was kept for further study. In addition, any filter which accumulated water or secretions during the 24 hours was replaced and its resistance measured.

Microbiological evaluation of ventilators

The ventilators were disinfected and their autoclavable parts sterilised before the study was started. The ventilators were then checked for contamination as follows. A clinically clean tubing system was connected to the ventilator and an Olympic Aero-Test sampler (Fig. 2) connected to the patient Y-piece via a clinically clean catheter mount. The ventilator controls were set to maximum airway pressure and a high minute volume (e.g. V_T 1 litre, f 20 breaths/minute). The ventilator was then run for 2 hours. The sampler was removed and the agar plate (tryptone soya agar) incubated for 5 days at 37°C; microbial growth was checked at 24-hour intervals. Any bacteria cultured were identified. Sampling of expired gases leaving the ventilator during clinical use, was performed as follows. One hour before the filter change the check valve was removed from the ventilator port and a length of clinically clean tubing attached. An Olympic Aero-Test sampler was connected to the tubing and left in place during filter changing and for 1 hour afterwards. The sampler agar plate was incubated and examined as above.

When a patient's ventilator therapy ceased, the disposable tubing was double-clamped at either end of each limb with umbilical clamps, and the

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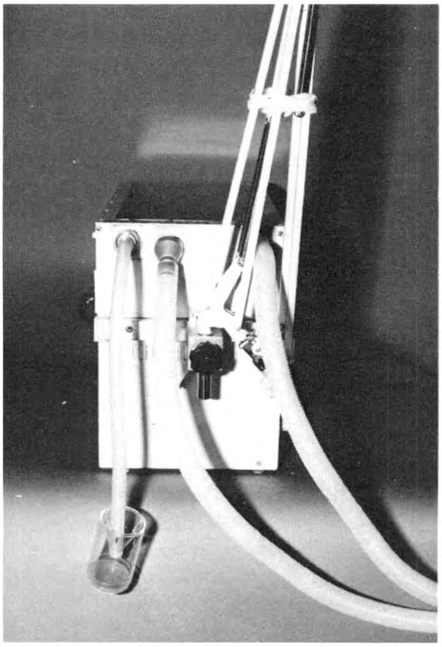

Fig. 2. Olympic Aero-Test sampler in use.

limbs labelled 'inspiratory' and 'expiratory'. The tubing was sent to microbiology where each limb was aseptically rinsed with 50 ml of 0.25 strength Ringer's solution. Four aliquots of 20 ml were withdrawn and filtered through four separate 0.45-μm filter discs. The filters were placed on two cysteine–lactose–electrolyte-deficient agar plates and two chocolate-blood agar plates before incubation for 5 days at 37°C. Lengths of unused tubing were processed using the same protocol as controls. Sampling efficiency was measured by the use of lengths of unused tubing contaminated with known amounts (10–10^6 colony forming units) of a reference bacterium (Oxford *Staphylococcus aureus* NCTC 6571) and subjected to the above sampling procedure.

The ventilators were checked at the end of the study using Olympic Aero-Test samplers as outlined above.

Results

The results are summarised in Table 1.

Aero-Test samplers

Ventilators. Before the study began, all seven ventilators were tested after they had been disinfected and their autoclavable parts sterilised; one plate yielded skin flora (one colony of a diphtheroid). Whenever a ventilator was serviced it was retested after decontamination; one plate yielded an environmental organism (one colony of *Bacillus* species).

At the end of the study the ventilators were retested; four plates grew less than five environmental organisms each, mainly *Bacillus* species.

Expired gases. Thirty-five plates were received, of which 16 yielded no growth. Ten plates yielded environmental organisms (*Bacillus* species and various gram-positive cocci) while nine plates yielded nonpathogenic skin flora (mainly coagulase-negative staphylococci).

Tubing

Half of the clinically clean unused tubing yielded environmental organisms (*Bacillus* sp.) and skin flora (diphtheroids). In the laboratory experiments to measure sampling efficiency, 95% of the Oxford *S. aureus* was recovered from the tubing.

Table 1. Microbiological results. Incidence of various types of bacterial growth.

	No growth	Environmental		Skin flora		Mixed flora		Respiratory pathogens	Total (plates)
Colony counts/plate		*<5*		*<2*	*>100*				
Aero-Test samplers									
Ventilators									
Pre-study	6	0		1	0	0		0	7
Post-study	3	4		0	0	0		0	7
Expired gases	16	10		8	1	0		0	35
Colony counts/plate		*<20*	*20–100*	*<5*		*<15*	*>100*		
Tubing									
Inspiratory	14	11	4	1		2	0	0	32
Expiratory	15	10	5	0		1	1	0	32
Total	29	21	9	1		3	1	0	

Thirty-two sets of tubing were received (four patients were each ventilated for two periods). The results of sampling are summarised in Table 1. Ten sets were completely sterile and one limb of a further nine sets was also sterile. The remaining tubing yielded only nonpathogenic organisms. Organisms were predominantly environmental in origin; the most frequently isolated was *Bacillus* sp. The skin flora consisted mainly of diphtheroids but included coagulase-negative staphylococci. In four instances *Bacillus* species were isolated from consecutive sets of tubing from the same ventilator.

Growth on the Aero-Test sampler plates only once matched growth obtained from the tubing. There was no significant difference in the numbers or types of organisms isolated from inspiratory as compared with expiratory limbs. Increased duration of ventilation was not associated with the isolation of increased numbers of bacteria.

Patients

The nosocomial infection record for the period of the study (January–June 1985) was compared to the record for the same 5-month period in 1984. During the study period, when the HME filter was used, 384 patients were admitted to the ITU; 75 were ventilated and the respiratory tracts of 16 were either colonised or infected with *Pseudomonas aeruginosa*. In the comparable period January–June 1984, when conventional breathing systems and hot water bath humidifiers were used, 380 patients were admitted to the ITU; 66 were ventilated and the respiratory tracts of 35 yielded *P. aeruginosa*.

Resistance measurements

Resistance to airflow at 50 litres/minute (kPa/litre/second) was measured in 128 filters. The resistance was less than 0.12 kPa/litre/second on 125 occasions. In one instance, when the filter had been removed from the airway of a patient with left ventricular failure and pulmonary oedema, the resistance was 0.198 kPa/litre/second. On two occasions in a patient with acute respiratory failure, resistance *R* lay between 0.12 and 0.18 kPa/litre/second.

Discussion

The present study demonstrates that these filters provide an efficient barrier to bacteria *in vivo* and prevent the contamination of respiratory apparatus with human pathogens. There was no build-up of organisms in the ventilators during the study period and no pathogens were isolated from them or from sampler plates used while patients were ventilated. Those plates which yielded environmental or normal human skin organisms may have reflected contamination that occurred during manipulation of the equipment. Some sets of tubing yielded nonpathogenic environmental organisms; these organisms may have been present in the clinically clean, but not sterile, tubing or may have been introduced during the rare introduction of an oxygen analyser. It was therefore concluded that the routine disinfection and sterilisation of ventilators was no longer necessary. Isolation of the patient from the ventilator by a HME filter protects the patients from pathogens which may be harboured in ventilators,[8–12] and further contamination of equipment by the patient is prevented. The expulsion of pathogens into the atmosphere ceases, so that secondary infection of other ITU patients, who are particularly vulnerable to nosocomial infections,[13,14] is decreased. In our ITU the proportion of patients whose respiratory tract was colonised or infected by *P. aeruginosa*, was reduced following the introduction of HME filters; this was felt to be an important step in reducing the risk of nosocomial infection by this organism. The use of water bath type humidifiers has also been shown to create reservoirs for infection,[15,16] and the isolation of patient and ventilator from this source requires filters at the inspiratory and expiratory ports and between patient and humidifier. In our study one Pall Ultipor Heat and Moisture Exchanging Filter was used at the Y-piece as the means of humidification and as a bacterial filter. The bacterial filtration properties of this HME filter in this position appear to prevent the contamination of the breathing system, unlike simple HMEs which offer no barrier to bacteria and may even harbour pathogens.[17–19] In this study the Pall Ultipor Filter also served as an HME in patients who required long-term ventilation. The optimal requirements for such an HME are not known but a recent American publication[20] suggests that an output of 21–24 mg H_2O/litre ventilation at 27–29°C is sufficient to prevent pulmonary damage during artificial ventilation. The BB50T HME filter has an output[2] of 24 mg H_2O/litre at

31°C and Chalon[3] has confirmed this in patients who have undergone abdominal surgery.

An increase in resistance to ventilation due to a filter was reported by Buckley.[6] This was not confirmed in our study, despite long-term use of these filters. In Buckley's[6] report the filters were used with heated water bath humidifiers and, due to incorrect positioning of one of the filters, it became filled with water. Many of our patients had either pulmonary oedema or pneumonia with sputum production and in only one case did a filter fill with secretions. This was easily seen through the transparent case of the filter and, after emptying, the resistance of the filter measured less than 0.12 kPa/litre/second. The use of nebulised drugs and saline installation caused no problems. A recent Hazard Notice from the Department of Health[21] reported an incidence of blocked filters when used in the expiratory limb of breathing systems in conjunction with ipratropium bromide water and saline aerosols. Our practice has been to disconnect the patient from the breathing system and ventilate manually during the administration of nebulised drugs.

The HME filter offers several important advantages when used in intensive care. Its particular value, demonstrated in this study, is in the isolation of patient from ventilator such that we now feel there is no need to decontaminate ventilators after use by patients. In this ITU, this has resulted in reduced labour and equipment costs and the release of cleaning areas for storage space. Use of the filter in this study and subsequently, indicates that it is an efficient humidifier for use in patients who require long-term ventilation and avoids the serious hazards presented by water bath humidifiers. It is also much preferred by nursing staff for its simplicity and safety.

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Arterial to end-tidal carbon dioxide tension difference during anaesthesia for tubal ligation

K. BHAVANI SHANKAR, H. MOSELEY, Y. KUMAR, V. VEMULA AND A. KRISHNAN

Summary

Twenty-nine patients scheduled for postnatal tubal ligation by minilaparotomy under general anaesthesia were studied. Arterial and end-tidal carbon dioxide tensions were determined during anaesthesia. The mean arterial to end-tidal carbon dioxide tension difference was 0.08 kPa (SEM 0.05). Thirty-one percent of the patients had negative values. These results were similar to those observed during Caesarean section. The physiological changes responsible for reduced arterial to end-tidal carbon dioxide values, persist into the postnatal period. It is predicted from the regression analysis of the time between delivery and anaesthesia for tubal ligation and arterial to end-tidal CO_2 *difference, that the values might return to normal nonpregnant levels by 8 days following delivery.*

Key words

Measurement techniques; capnography.
Anaesthesia; obstetric.

Arterial to end-tidal carbon dioxide tension difference, $(a - E')P\text{CO}_2$, has been measured in nonpregnant subjects during anaesthesia and various values have been quoted: Nunn and Hill,[1] 0.63 kPa (SD 0.33); Fletcher and Jonson,[2] 0.6 kPa at small tidal volumes (with 5th and 95th percentiles of 0.20 and 1.40 kPa) and 0.3 kPa at large tidal volumes (with 5th and 95th percentiles of −0.10 and 1.10 kPa); Takki *et al.*,[3] 0.46 kPa (SEM 0.26); Askrog *et al.*,[4] 0.66 kPa (SEM 0.36); Raemer *et al.*,[5] 0.54 kPa. It has been observed that, during Caesarean section, the $(a - E')P\text{CO}_2$ value was reduced and that $P\text{aCO}_2$ was closer to $P\text{E}'\text{CO}_2$ than in nonpregnant subjects.[6,7] This was attributed to the various physiological changes that are associated with pregnancy.

Therefore, it was decided to investigate whether this relationship was limited to pregnant patients who undergo anaesthesia for Caesarean section, or continued during general anaesthesia in the postnatal period. The study was planned to evaluate the $(a - E')P\text{CO}_2$ difference during anaesthesia for tubal ligations in the postnatal period.

Methods

The study was approved by the hospital ethical committee and informed consent was obtained from all patients. It comprised 29 patients scheduled for tubal ligation by minilaparotomy following spontaneous vaginal delivery; carbon dioxide insufflation into the peritoneum was not used. All patients were nonsmokers and had no previous respiratory or cardiac abnormalities.

K. Bhavani Shankar, MD, Consultant, H. Moseley, FFARCS (Eng.), Senior Consultant and Lecturer, Y. Kumar, MD, Consultant, V. Vemula, MB, BS, DA, A. Krishnan, MB, BS, DA, Registrars, Department of Anaesthesia and Intensive Care, Queen Elizabeth Hospital, Barbados, West Indies.

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All patients were unpremedicated. Anaesthesia was induced with thiopentone 5 mg/kg and tracheal intubation performed following suxamethonium 1.5 mg/kg. Anaesthesia was maintained with a mixture of 30% oxygen in nitrous oxide and 1–1.5% halothane. Pethidine 1 mg/kg was given for additional analgesia and pancuronium 0.08 mg/kg for muscle relaxation. The lungs were ventilated with a Seimens Elema Servo ventilator (Model 900 B). Patients received a minute volume of 100 ml/kg/minute at a frequency of 12 breaths/minute (tidal volume 8.33 ml/kg).

The end-tidal carbon dioxide concentration was measured continuously at the proximal end of the tracheal tube using a Puritan–Bennett/Datex CO_2 monitor. The analyser was calibrated at regular intervals to read carbon dioxide concentrations in 70% nitrous oxide, using a known concentration of carbon dioxide. Capnograms were recorded continuously with the Puritan–Bennett/Datex CO_2 recorder which was also calibrated by recording a calibration signal prior to each use. The speed of the capnogram recording was 500 mm/minute (±3%). Arterial blood was sampled from the left radial artery 25 minutes after induction of anaesthesia. The sample was analysed immediately for $Pa\text{CO}_2$ in a Corning blood gas analyser (Model 165/2) after two-point calibration before each measurement, at 37°C. Nasopharyngeal temperature was monitored by a calibrated thermometer in all patients and the blood gas results were corrected to body temperature using the nomograms of Kelman and Nunn.[8] The end-tidal carbon dioxide concentrations recorded at the time of the arterial sampling, were corrected to body temperature and then converted to kPa.

The fraction (f) of end-tidal gas from unperfused alveoli was calculated using the equation of Nunn and Hill:[1]

$$f = \frac{(Pa\text{CO}_2 - P\text{E}'\text{CO}_2)}{Pa\text{CO}_2}$$

Table 1. Patient data and $P\text{CO}_2$ values.

Age (years)	Postdelivery time (hours)	$Pa\text{CO}_2$ (kPa)	$P\text{E}'\text{CO}_2$ (kPa)	$(a - \text{E}')P\text{CO}_2$ (kPa)
33	96	3.75	3.68	0.07
28	45	3.45	3.18	0.27
40	36	3.90	3.89	0.01
32	10	3.28	3.44	−0.16
32	12	3.63	3.53	0.10
24	30	3.35	3.62	−0.27
29	30	3.13	3.46	−0.33
22	36	4.07	3.79	0.28
44	36	3.52	3.43	0.09
35	36	3.80	4.17	−0.37
32	40	4.21	3.88	0.33
23	38	4.10	3.79	0.31
33	80	3.52	3.13	0.39
25	144	3.83	3.32	0.51
44	18	2.97	3.31	−0.34
23	20	2.68	3.13	−0.45
29	42	3.41	2.73	0.68
29	77	3.76	3.40	0.36
27	40	3.95	3.69	0.26
32	54	4.16	4.05	0.11
32	42	3.70	3.86	−0.16
24	46	4.15	3.97	0.18
26	36	3.52	3.40	0.12
28	24	3.84	4.14	−0.30
33	46	3.31	3.50	−0.19
26	96	3.70	3.50	0.20
31	31	4.24	3.96	0.28
29	102	4.01	3.96	0.05
32	116	3.70	3.34	0.36
Mean (SEM)				
30.24 (1.04)	50.31 (6.09)	3.67 (0.07)	3.59 (0.06)	0.08 (0.05)

A paired t-test was used to evaluate the statistical difference between mean Pa_{CO_2} and mean $P_{E'CO_2}$ (the data were normally distributed). Regression analysis was done between Pa_{CO_2} (independent variable, x) and $P_{E'CO_2}$ (dependent variable, y) and the parameters of the regression equation and confidence limits were determined. Since $(a - E')P_{CO_2}$ is dependent on postdelivery time (the time between delivery of the baby and time at which general anaesthesia was given, here calculated in hours), a further regression equation was determined between postdelivery time (independent variable, x) and $(a - E')P_{CO_2}$ (dependent variable, y). Linear, curvilinear and semilogarithmic regressions were tried in order to determine which would give the best fit to the data.

Results

The mean weight of the subjects in the group studied was 72.17 kg (SEM 2.47). Table 1 shows the age, postdelivery time and Pa_{CO_2}, $P_{E'CO_2}$ and $(a - E')P_{CO_2}$ values for all subjects, together with their mean values and standard errors. There was no statistically significant difference between mean Pa_{CO_2} and mean $P_{E'CO_2}$ (paired t-test).

Table 2 shows the regression equations, together with r values, p values and confidence limits, between Pa_{CO_2} (x) and $P_{E'CO_2}$ (y) and between postdelivery time (x) and $(a - E')P_{CO_2}$ (y). Curvilinear regression between postdelivery time (x) and $(a - E')P_{CO_2}$ (y) did not improve the fit of the curve, whereas semilogarithmic regression (log duration (x) and $(a - E')P_{CO_2}$ (y)) showed only marginal improvement of r by 0.02. Linear regression was therefore considered the best predictor of $(a - E')P_{CO_2}$ values at various postdelivery times. The fraction of end-tidal gas from unperfused alveoli was 0.02 (SEM 0.01). The mean tidal volume used was 571 ml (SEM 19).

Discussion

The mean arterial to end-tidal carbon dioxide difference, during anaesthesia for postnatal tubal ligation, was 0.08 kPa (SEM 0.05). There was no statistically significant difference between Pa_{CO_2} and $P_{E'CO_2}$ and hence the latter might reflect Pa_{CO_2}. It was observed previously by Shankar *et al.*[6] that, during Caesarean section, Pa_{CO_2} was very close to $P_{E'CO_2}$. Similar observations were made by Burger *et al.*[7] during assessment of the amount of non-rebreathing ventilation required to maintain Pa_{CO_2} of 4.26 kPa during Caesarean section. The mean $(a - E')P_{CO_2}$ value observed by Shankar *et al.*[6] during Caesarean section, was 0.10 kPa (SEM 0.08). No significant difference was found between the $(a - E')P_{CO_2}$ values observed during Caesarean section and post-delivery tubal ligation in the present study.

Our results show that $(a - E')P_{CO_2}$ is very small and Pa_{CO_2} is close to $P_{E'CO_2}$ even in the postdelivery period. The physiological changes of pregnancy, such as increased cardiac output, increased blood volume and haemodilution, that result in better perfusion of alveoli, persist into the postdelivery period and account for the low $(a - E')P_{CO_2}$ values observed.[6,9,10] The fraction of end-tidal gas from the unperfused spaces was calculated as 0.02 kPa (SEM 0.01) in this study, which is similar to the 0.01 kPa (SEM 0.02) observed during Caesarean section. This fraction is significantly less ($p < 0.001$) when compared to the 0.19 kPa (SEM 0.01) observed in non-pregnant patients under anaesthesia (our unpublished observations).

The $(a - E')P_{CO_2}$ values in 31% of our patients were negative, when $P_{E'CO_2}$ exceeded Pa_{CO_2}. During Caesarean section the $(a - E')$-P_{CO_2} values were found to be negative in 50% of instances.[6] Burger *et al.*[7] observed similar negative $(a - E')P_{CO_2}$ values in 14 out of 18 patients undergoing Caesarean section, with a mean $(a - E')P_{CO_2}$ of -0.09 kPa (SEM 0.03).

Table 2. Results of regression analyses.

Independent variable (x)	Dependent variable (y)	Correlation coefficient (r)	Regression equation	Confidence interval of b (at p = 0.05)
Pa_{CO_2}	$P_{E'CO_2}$	0.693**	$\hat{Y} = 0.615\ x + 1.34$	0.355–0.874
Postdelivery time (hours)	$(a - E')P_{CO_2}$	0.495*	$\hat{Y} = 0.004\ x - 0.140$	0.001–0.007

* $p < 0.01$.
** $p < 0.001$.

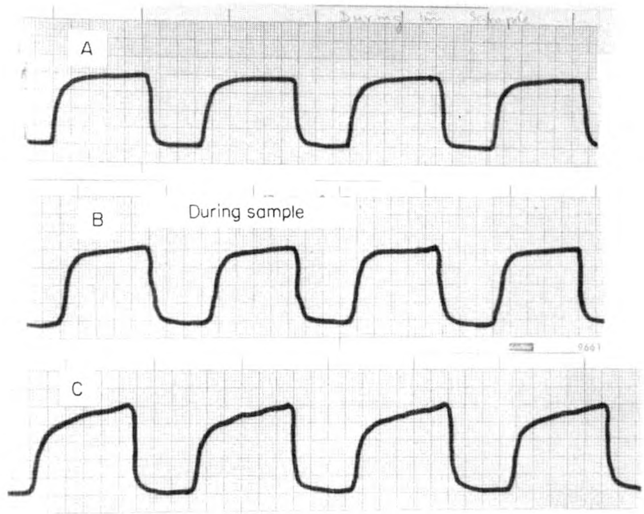

Fig. 1. Capnogram A, during general anaesthesia in nonpregnant female, (a − E′)PCO$_2$ 0.7 kPa; capnogram B, from present study, (a − E′)PCO$_2$ 0.33 kPa; capnogram C, from present study, (a − E′)PCO$_2$ −0.33 kPa. Capnogram C shows a steeper phase III slope compared to A and B, which results in end-tidal exceeding mean spatial and temporal alveolar PCO$_2$.

Negative or zero (a − E′)PCO$_2$ values were also observed in 12% of nonpregnant patients under anaesthesia, by Fletcher and Jonson.[2] They postulated that such values may be due to the temporal mismatching of ventilation–perfusion that occurs with low frequency, high tidal volume ventilation. This results in a positive slope of phase III of single breath test for carbon dioxide tracings (plots of expired PCO$_2$ *versus* tidal volume), as shown in Fig. 1. Therefore, PE′CO$_2$ exceeds spatial and temporal mean alveolar carbon dioxide tension.[2,11] The higher incidence of negative (a − E′)PCO$_2$ values during Caesarean section compared to that in nonpregnant patients, is due to the reduced functional residual capacity and increased carbon dioxide production that are associated with pregnancy.[6] The reduced functional residual capacity and increased carbon dioxide production of pregnancy return towards normality in the postdelivery period,[9] which explains the lower incidence of negative (a − E′)PCO$_2$ values during postdelivery tubal ligation than during Caesarean section.

By using the regression analysis between postdelivery time (x) and (a − E′)PCO$_2$ (y), it is predicted that at 168 hours (7 days postdelivery) the (a − E′)PCO$_2$ value would be 0.53 kPa and at 192 hours (8 days postdelivery), 0.62 kPa. Normal nonpregnant values have been reported as 0.63 kPa (SD 0.33),[1] 0.66 kPa (SEM 0.36)[4] and 0.54 kPa.[5] Therefore it is probable that, by 8 days, the (a − E′)PCO$_2$ values would return to normal nonpregnant values, although the physiological changes such as increased cardiac output and increased ventilation return to normal values only by 2 weeks following delivery.[9] However, taking into consideration the range of confidence intervals of the regression coefficient b (Table 2), this predicted interval might also be as long as 2 weeks.

Acknowledgments

We are grateful to Professor J. Homi, FFARCS, Head of the Department of Anaesthesiology and Intensive Care, University of West Indies, Mona, Jamaica, West Indies, for making available to us the Datex CO$_2$ monitor and recorder. We wish to thank Dr P. Seshagiri Rao, PhD, for his assistance in statistical evaluation of the data and also the Department of Obstetrics of the Queen Elizabeth Hospital for their cooperation in carrying out this study.

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Anaesthesia, 1987, Volume 42, pages 487–490

Difficult tracheal intubation: a retrospective study

G. L. T. SAMSOON AND J. R. B. YOUNG

Summary

This is a retrospective study of patients whose tracheas were impossible to intubate on a previous occasion. There is a correlation between the degree of difficulty and the anatomy of the oropharynx in the same patient. The study was initially on obstetric patients but was extended to nonobstetric surgical patients in order to increase the number of cases investigated. The incidence of failed intubations in the obstetric group over a 3-year period was seven out of 1980 cases, whereas in the surgical group the results were six out of 13 380 patients. Any screening test which adds to our ability to predict difficulty in intubation must be welcomed, as failure to intubate can potentially lead to fatality.

Key words

Intubation, tracheal; difficult.

Failed or difficult tracheal intubation is, fortunately, a comparatively rare occurrence. The outcome varies from mere nuisance value, to potentially life-threatening situations or death.[1] Successive generations of anaesthetists have been taught over the years to anticipate difficult intubations from various anatomical factors, such as short thick neck, protruding incisors or high arched palate.[2,3] Despite this, a number of perfectly normal-looking patients still present us with the greatest difficulties, quite unexpectedly.

This paper was prompted by two such cases. We consider that any non invasive clinical test which could identify those patients at risk, would be of immense benefit to all anaesthetists. The objective of this paper is to indicate that such a test may be available.[4]

Methods

Difficult intubation is defined as inadequate visualisation of the glottis, and failed orotracheal intubation as inability to insert a tracheal tube from the oropharynx into the trachea. For the purpose of this study, patients from our obstetric register between 1982 and 1985 known to have had failed intubation, were recalled for assessment. In view of the small number of patients involved, the study was expanded to include patients from other surgical lists during the same period.

An assessment of the airways was carried out based on the method described by Mallampati *et al.*[4,5] The patients sit upright with the head in the neutral position. They are asked to open their mouth as widely as possible and to protrude their tongue to a maximum. The observer sits opposite at eye level and, with a pen torch, inspects the pharyngeal structures. The airway is then classified according to the structures seen, as follows: class I, soft palate, fauces, uvula, pillars; class II, soft palate, fauces, uvula; class III, soft palate, base of uvula; class IV, soft palate not visible at all (Fig. 1).

G.L.T. Samsoon, MD, FFARCS, Registrar, J.R.B. Young, FFARCS, Consultant, St Mary's Hospital, Portsmouth, Hampshire.

Correspondence should be addressed to Dr J.R.B. Young, Forest Hill, 65A Links Lane, Rowlands Castle, Hants PO9 6AF.

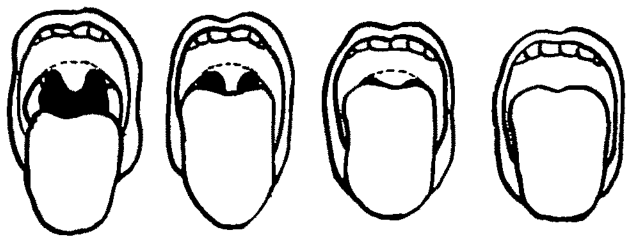

Fig. 1. Pictorial classification of the pharyngeal structures as seen when conducting the tests, modified from Mallampati *et al.*[4,5] Note: Class III, soft palate visible; class IV, soft palate not visible.

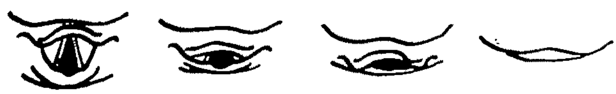

Fig. 2. Laryngoscopic views obtained by modifying the drawings used by Cormack and Lehane[6] in their original classification.

The patient is then allowed to relax for one minute and the test repeated to confirm the classification. In our patients, photographs were also taken, and were shown to an independent ear, nose and throat surgeon who made the classification.

The view obtained at laryngoscopy was graded according to the description of Cormack and Lehane:[6] grade I, full view of glottis; grade II, only posterior commissure visible; grade III, only tip of epiglottis visible; grade IV, no glottis structure visible (Fig. 2).

Results

During the period investigated, namely 1982–85, seven obstetric patients from a total of 1980 could not be intubated, giving an incidence of 1:280. All those patients were shown retrospectively to have class IV airways, with the exception of one mother (class II) who proved to have tracheal stenosis (Table 1).

Within the same period of time, six surgical patients from a total of 13 380 could not be intubated, giving an incidence of 1:2230. All these were unexpected, and all were shown to have class IV airways (Table 2).

Discussion

Mallampati[4] reported the association of difficult intubation and concealment of the soft palate by the base of the tongue. However, credit must be given to Skolimowski *et al.*[7] who, in a case of failed intubation in a micrognathic patient, described the following: 'the anteroposterior dimension of the pharynx was markedly reduced

Table 1. Failed obstetric intubations.

Patient	Intubation risk	Preclinical assessment (Class)	Laryngoscopy (Grade)
Primipara, 25 years, emergency LSCS	Not expected	IV	IV
Primipara for ELSC, footling breech	Not expected	II	I
Primipara with compound presentation, emergency LSCS	Not expected	IV	III
Primipara with foetal distress	Not expected	IV	III
Primipara for LSCS, failure to progress	Not expected	IV	III
Primipara, 46 years, elective section	Not expected	IV	III–IV
Primipara, 28 years, elective section	Not expected	IV	III

LSCS, lower segment Caesarean section; ELSC, elective lower segment Caesarean section.

Table 2. Failed intubations in nonobstetric surgical patients.

Patient	Intubation risk	Preclinical assessment (Class)	Larynogoscopy (Grade)
Male, 34 years, urethral obstruction	Not expected	IV	III
Male, 45 years, mastoid	Not expected	IV	III
Female, 49 years, hysterectomy	Not expected	IV	III
Female, 29 years, wisdom teeth	Not expected	IV	III
Female, 24 years, laparoscopy	Not expected	IV	III
Male, 24 years, urethroplasty	Not expected	IV	III

by a large tongue reaching far posteriorly. It was not possible to examine the lower pharynx by means of a laryngoscope mirror because the tongue was situated too far posteriorly to be pulled forward'. In effect, Skolimowski described these signs but did not specifically relate them to difficult intubation.

Certain conditions must be fulfilled for successful intubation under direct vision. There should be adequate flexion of the lower cervical vertebrae, and extension of the head at the atlanto-occipital joint which brings the oropharyngeal cavity into line with the pharyngolaryngeal cavity.[8] Ability to open the mouth[9] is essential to permit the introduction of the laryngoscope, as well as a pharyngeal cavity adequate to facilitate laryngoscopic view.[10,11]

The tests described above were conducted at the time of the pre-operative visit and, therefore, effectively before the induction of anaesthesia. They give an idea of the adequacy of bite, the size of the tongue and the size of the oropharyngeal cavity. In effect, if the base of the tongue overhangs the larynx, the entrance to the glottis will appear more anterior.

None of our obstetric patients presented with any of the classical features associated with difficult intubation[2,3,12] and, although they were present in some of our patients from the surgical lists, they were usually mild, such that significant problems were not anticipated by the anaesthetists involved.

It is not generally appreciated that for a safe intubation, the tracheal tube must be seen to pass between the vocal cords. Grade III and IV laryngoscopies constitute blind intubation and, as such, carry a theoretical 50% risk of oesophageal intubation. From the last *Confidential Enquiry into Maternal Deaths* (1979–81), eight patients died of this complication. It has been reported that intubation for grade III laryngoscopy should be fairly easy. The majority of laryngoscopic views in this study fell into grade III and yet two patients were intubated only after repeated attempts. Grade IV laryngoscopy is rare. Cormack and Lehane[6] suggest an incidence of less than 1 per 100 000, but our experience suggests a higher incidence.

There is not a simple test to predict difficulty in tracheal intubation. Salem[13] mentioned that most difficult intubations can be predicted from anatomical criteria, but did not elaborate further. Our findings are similar to those of Tunstall,[14] in that most obstetric patients who prove difficult to intubate, more often than not have non-remarkable features. Furthermore, pregnancy leads to an increase in fatty deposits and water in soft tissues, which may modify facial features.[15]

The anaesthetic literature abounds with anecdotal reports dealing with difficult intubations, but techniques including retrograde cannulation or blind nasal intubation have no place in emergency obstetric situations. Anaesthetists must be aware that there are some obstetric patients whom they may never be able to intubate irrespective of their experience.

We believe that the above test[4,5] could be used to screen the population to identify those patients most at risk for difficult intubation. We consider those with class IV and possibly those with class III airways to be at risk. Classes I and II should not pose any serious problems unless there is limitation of extension of the head. Since we began this study, we have been so impressed by the positive correlation between the classification and the ease, or otherwise, of intubation, that in our obstetric department we most vigorously encourage early use of epidural analgesia in those classified as grades III and IV, in the hope that general anaesthesia may be avoided. Junior anaesthetic staff are encouraged to notify more senior colleagues should general anaesthesia be pending in these patients.

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Intrathecal morphine in aortic aneurysm surgery

I. DAVIS

Summary

The purpose of this study was to compare the peri-operative conditions produced by intrathecal morphine with those that result from conventional analgesia in aortic aneurysm surgery. Low-dose intrathecal morphine provides a level of analgesia during operation indistinguishable from that of moderate doses of parenteral opiate, but is no more effective in attenuating autonomic responses to the procedure. Analgesia is prolonged into the postoperative period, does not cause clinically evident respiratory depression and can be enhanced by small doses of intravenous opiate. The principal advantage of intrathecal morphine is the avoidance of irregular and inadequate pain relief in the early, and most painful, part of the postoperative period. Low-dose intrathecal morphine appears safe, effective and feasible in aortic aneurysm surgery and provides an alternative to traditional management with parenteral opiates.

Key words

Anaesthetic techniques; intrathecal narcotics.
Surgery; cardiovascular.

Intrathecal morphine (ITM) has been employed for more than 5 years and is known to produce prolonged and intense analgesia.[1–4] It is an easy technique to use but its application to major surgery has been inhibited by reports of delayed, sometimes profound, respiratory depression.[5–7] Lesser concerns, now mainly resolved,[8] have been the choice and dose of drug and the incidence of minor side effects. There remains a dearth of comparisons of ITM with traditional techniques in respect of effectiveness, safety and feasibility.[9] The present study compares low-dose ITM, which we have found satisfactory for upper abdominal operations,[10] with balanced anaesthesia in aortic aneurysm surgery. Aneurysmectomy was chosen because it is an extensive and painful intervention carried out on a notably unhealthy population[11] and necessitates close intra- and postoperative observation. The indicators chosen for assessment of the techniques were peri-operative stability indicated by the extent of variation in pulse rate, systolic blood pressure and rate–pressure product over the observation period, the incidence of complications during and after surgery, and the quality of intra- and postoperative analgesia.

Patients and methods

Thirty male patients who presented for aortic aneurysm surgery, who were in sinus rhythm, were not taking beta-adrenoreceptor blocking drugs or calcium antagonists and had not sustained a recognised myocardial infarction in the preceding 6 months, were randomly assigned to two groups, A and B, which were treated identically except for the analgesic regimen. The study

I. Davis, MB, BS, FFARCS, Consultant, Worcester Royal Infirmary, Newtown Road, Worcester WR5 1HN.

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was approved by the district ethical committee and, after assignment to group A or B, informed consent was obtained from the patient on the day before operation. All patients were in ASA grades 2 or 3 and all were given a premedication of 5–15 mg diazepam orally 60–90 minutes before induction of anaesthesia. All were pre-oxygenated for 5 minutes before anaesthesia was induced with thiopentone 2–4 mg/kg body weight. Muscle relaxation was produced by alcuronium 0.25 mg/kg and the patient's lungs were ventilated for 5 minutes with 50% oxygen in nitrous oxide plus 0.5% halothane before tracheal intubation. All were then ventilated using the same mixture in order to achieve an end tidal carbon dioxide concentration of 5–6% during surgery. Additional doses of muscle relaxant (about a quarter of the intubating dose) were given hourly and surgery was performed with a 10° head-down tilt.

Monitoring consisted of direct arterial and central venous pressure display with electrocardiography using the CM5 configuration. Patients were positioned on a circulating-water heater maintained at 35°C and all intravenous fluids were warmed. Fluid replacement for insensible loss consisted of Hartmann's solution 10 ml/kg/hour, and volume replacement was achieved with modified gelatin solution, red cell concentrate and whole blood to maintain a constant central venous pressure throughout the operation. Residual muscle relaxation was reversed by means of atropine and neostigmine in conventional dosages.

Patients in group A were given an intrathecal injection of 0.8 mg preservative-free morphine in 4 ml of 0.9% saline, without barbotage, at the L_{2-3} level through a 25-G needle immediately before pre-oxygenation: they received no further analgesia in theatre. The patients in group B were given papaveretum 0.1 mg/kg by slow intravenous injection during pre-oxygenation and additional doses of the same drug during surgery to a total dose of 0.25–0.5 mg/kg depending upon body weight and pre-operative condition: the mean dose (standard deviation) was 30 (10) mg with a range of 10–40 mg.

All patients spent the first 24 hours after surgery in a high-dependency unit. Group A patients who felt pain were given papaveretum 2 mg intravenously without restriction on the frequency of administration. Group B patients in pain were given papaveretum 0.25 mg/kg by intramuscular injection, again without restriction on the frequency of administration. All patients received 35% oxygen from a high-volume injector-driven mask until the morning after operation. Volume replacement was guided by maintenance of a constant, low-normal central venous pressure of -5 to 0 cm H_2O measured from the sternal angle.

Patients were assessed hourly for pain and were graded 'asleep or pain-free' or 'in pain': those in pain were treated. Hourly basic observations were made and a respiratory rate of less than 10 breaths/minute was taken as the indication for naloxone administration. All patients had indwelling bladder catheters so the incidence of urinary problems could not be assessed: otherwise, patients were monitored for cardiac dysrhythmias and potential side effects of treatment. After 24 hours all patients in pain were treated with intramuscular papaveretum as for group B.

Pulse rates were taken by palpation, blood pressures by oscillotonometry (for consistency, even though direct measurement was used in theatre and sometimes longer) to the nearest 5 mmHg and rate–pressure products during surgery were calculated whenever the electronic monitor indicated an increase. Values for analysis were those taken before pre-oxygenation, at the time of maximal rate–pressure product during operation, and the maximum value from the hourly postoperative observations in the high-dependency unit.

Results

Five patients were lost from the study: one assigned to group A preferred not to have an intrathecal injection, notes of two were incomplete in a major respect, one patient died on the table from an insoluble surgical problem and one was found to have a resectable large-bowel tumour so aneurysmectomy was postponed. Details of the remaining 25 patients are shown in Table 1. There was no significance in the differences between groups when subjected to Student's *t*-test.

Changes in pulse rate, systolic blood pressure and rate–pressure product are shown in Table 2 where again analysis of differences was by Student's *t*-test. In each group the maximum intra-operative rate–pressure product showed a significant increase over the pre-operative value:

Table 1. Details of patients: values expressed as mean (SD).

	Group A	Group B	Difference
n	13	12	NS
Age, years	65.6 (9.5)	53.8 (19.8)	NS
Range	47–79	39–76	
Weight, kg	70.7 (12.3)	67.6 (13.3)	NS
Range	40–88	38–82	
Pulse rate, beats/minute	82 (12)	81 (10)	NS
Range	55–100	60–96	
Systolic BP, mmHg	149 (20)	158 (23)	NS
Range	120–200	130–215	
Haemoglobin, g/dl	14.9 (1.5)	13.5 (3.6)	NS
Range	11.5–17.0	10.7–17.0	
ASA grades 2/3	8/5	5/7	NS

Table 2. Variation in pulse rate (P), systolic blood pressure (BP) and rate–pressure product (RPP): values expressed as mean (SD).

	Group A			Group B			Difference
	P, beats/minute	BP, mmHg	RPP	P, beats/minute	BP, mmHg	RPP	
Pre-operative value	82 (12)	149 (20)	12 146 (2038)	81 (10)	158 (23)	12 723 (2151)	NS
Range	55–100	120–200	8 800–15 040	60–96	130–215	9600–15 910	
Intra-operative maximum	90 (9)	167 (20)*	15 121* (2043)	92 (14)*	167 (24)	15 352* (2998)	NS
Range	78–104	130–200	10 400–17 680	72–120	130–215	11 520–19 780	
Postoperative maximum	75 (10)*	155 (24)	11 631* (1922)	82 (13)	145 (15)*	11 881* (2673)	NS
Range	56–90	120–200	7000–14 800	54–100	125–180	7020–16 020	

* Significant change from preceding value; $p < 0.05$ taken as the level of significance.

in group A there was a significant increase in systolic blood pressure and in group B a significant increase in pulse rate. There was a significant decrease in both groups from the intra-operative maximum rate–pressure product to the maximum value found in the first post-operative day. In every case the maximum intra-operative rate–pressure product was found at the time of reversal of relaxation and not at either tracheal intubation or cross-clamping of the aorta. In group A the maximum postoperative pulse rate was significantly less than the intra-operative value, while in group B the maximum postoperative systolic pressure was significantly reduced from the intra-operative value. In both groups there was no difference between pre- and postoperative values of the indicators, nor were there between-group differences at the same stage.

No intra-operative complications attributable to the analgesic regimens were observed. All patients appeared pink and well-perfused, all secreted urine at a rate of at least 0.5 ml/kg/hour during the operation without diuretics, and no movements or sweating were seen. No sudden changes in pulse rate or systolic pressure were noted in response to surgical manoeuvres, and no patient developed either a dysrhythmia or change in ST segment level, even when rate–pressure products were maximal. Both the slowest and fastest heart rates, 54 and 120 beats/minute, were seen in group B patients. There was no appreciable difference in the duration of surgery, which was 144 minutes (SD 41) in group A and 149 minutes (SD 42) in group B.

In the postoperative period no patient in either group suffered clinically detectable respiratory depression (although no blood gas estimations were performed): no patient developed a respiratory rate of less than 10 breaths/minute, and naloxone was not used. Two patients in group A suffered facial itching but were not troubled by it. There was no vomiting in either group but one patient in group A, and two in group B, suffered nausea. One patient in group A developed a cough with sputum, and radiological signs of right basal consolidation: he had a

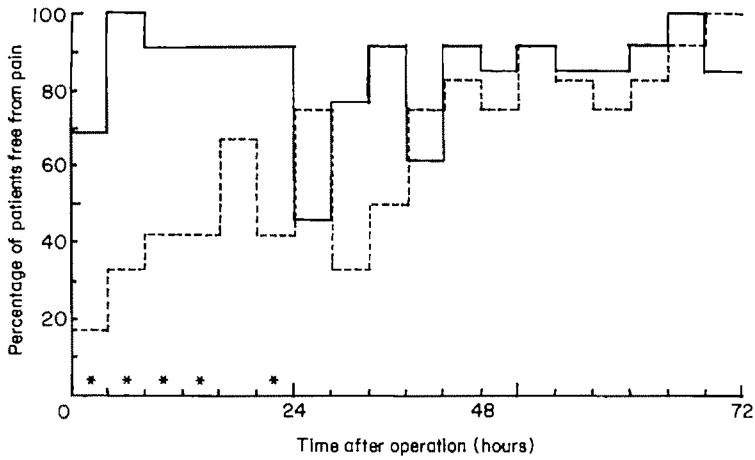

Fig. 1. Proportion of patients free of pain throughout each 4-hour period following surgery. The asterisks indicate differences significant at the $p < 0.05$ level. ——, Group A; ----, group B.

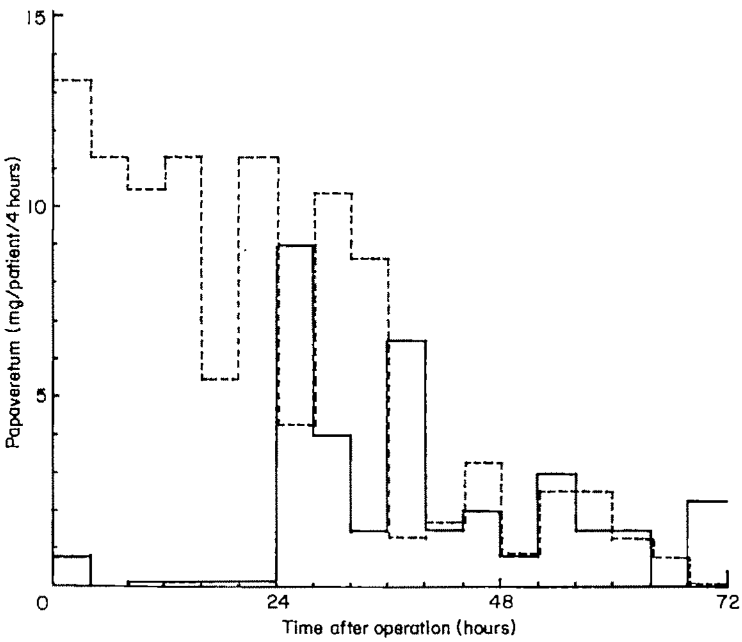

Fig. 2. Analgesic consumption per patient in each 4-hour period from the end of operation. ——, Group A; ----, group B.

symptomatic hiatal hernia and could have aspirated in the early postoperative period. Excluding the single on-table death, all patients survived their admission.

The two measures of the quality of postoperative analgesia were the proportion of patients who experienced (or claimed) freedom from pain throughout each successive 4-hour period from the end of the operation (Fig. 1), and the analgesic consumption in mg papaveretum per patient in each 4-hour period after surgery (Fig. 2). Group A patients had significantly better analgesia for five of the first six 4-hour periods after surgery (Chi-squared test with Yates' correction; $p < 0.05$ was taken as the level of significance). Analgesic consumption in group A patients was

small in the first postoperative day, at less than 1.5 mg papaveretum per patient, while group B patients required on average more than 63 mg papaveretum. On day 2 the figures were respectively 23.5 and 29.6 mg papaveretum, and on day 3, 9.1 and 7.9 mg. Differences on days 2 and 3 were not significant. There appears to be a rebound in analgesic consumption by group A patients in the early part of the second postoperative day (Fig. 2), yet 46% of the patients in the group remained pain-free.

Discussion

The intrathecal administration of opiates has a coherent theoretical and experimental history which begins with the gate control theory[12] of pain and proceeds with the detection[13] and mapping[14] of the opiate receptors to the discovery of the endogenous opiates.[15] Thence, by way of the demonstration of the analgesic activity of exogenous opiates applied to the animal cord,[16] to an *in vitro* model of a possible mechanism of action[17] which was later confirmed *in vivo*.[18] Intrathecal morphine was first used in man for the relief of intractable pain[19] and has since been employed for pain relief in obstetrics[3] and surgical analgesia,[20,4] although on a limited scale because of early reports of severe respiratory depression. This complication appears to be associated with higher dosages[6,7,21] and concomitant use of parenteral opiates, usually in premedication[6,4] but by no means always so.[20] Doses less than 1 mg given to patients who receive non-opiate premedication appear to be safe.[8,10] We have used a standard dose of 0.8 mg in 63 patients to date without clinical evidence of respiratory depression.

If the use of additional opiates in premedication and during surgery is avoided, does the pre-operative use of low-dose ITM provide adequate surgical analgesia? Detectable analgesia appears 10–15 minutes after the intrathecal injection of morphine and is maximal at 2–3 hours.[21] If it takes about 30 minutes from the start of anaesthetic induction to incision in elective aneurysm surgery (after the placement of adequate monitoring), analgesia should be established by the start of the operation and inadequate analgesia should result in detectable sympathetic activity. As the only difference between the two groups of patients was the analgesic regimen, and there were no appreciable between-group differences in maximal pulse rates, arterial blood pressures or rate–pressure products during surgery, low-dose ITM appears to provide analgesia equivalent to that of parenteral papaveretum in doses of 0.25–0.5 mg/kg (papaveretum 20 mg is equivalent to 15 mg morphine sulphate[22]).

The population which presents for aortic aneurysm surgery contains a high proportion of patients who suffer from hypertension and covert or overt ischaemic heart disease.[11] Surgery subjects them to risk factors known to exacerbate myocardial ischaemia, particularly intra-operative hypotension and a long abdominal operation[23] following intubation of the trachea.[24] A recent review[25] stresses the avoidance of hypoxaemia, tachycardia, hypertension, hypotension and especially combinations of these in the maintenance of a favourable myocardial oxygen supply/demand balance through the provision of adequate analgesia, normovolaemia and avoidance of hypocapnia during anaesthesia. The product of systolic blood pressure and heart rate, the rate–pressure product (RPP), is an index of myocardial oxygen demand[26] and a useful guide to the need for intervention.[27] Neither technique prevented the development, at the time of relaxant reversal, of RPPs significantly higher than pre-operative values. In group A the significant increase in systolic pressure appeared to be the principal contributor, while in group B the significant change in pulse rate appeared more important. The periods of maximal RPP must represent episodes of increased risk of ischaemic damage, since these patients must have a limited capacity to increase myocardial oxygen supply by increasing blood flow. In terms of stability of heart rate, glycopyrronium may be a better choice than atropine as an anticholinergic to administer with neostigmine.[28]

However, no changes in ST segment level, T-wave or incidence of extrasystoles were detected on the CM5 traces, even though some RPPs were close to 20 000—an unexpected result in view of the experience of others.[24] The changes in RPP at intubation and aortic cross-clamping were in the same direction, but not significantly different from pre-operative values. It is possible that the avoidance of hypocarbia,[29,30] use of halothane[31] and high $F\text{IO}_2$ exerted some cardioprotective effect.

In both groups RPP decreased after operation and maximum levels did not differ from pre-operative values. In group A the decrease in pulse

Table 3. Percentage changes in pulse rate (P), systolic blood pressure (BP) and rate–pressure product (RPP).

	Group A			Group B		
	P, beats/minute	BP, mmHg	RPP	P, beats/minute	BP, mmHg	RPP
Pre-operative value	100	100	100	100	100	100
Intra-operative maximum	110	112*	124*	114*	106	121*
Postoperative maximum	91*	104	96*	101	92*	93*

* Significant change from preceding value.

rate appeared to be the main contributor, and in group B the decrease in systolic arterial pressure dominated. Neither analgesic regimen appears to have contributed more than the other to the control of changes in RPP; these are shown as percentage changes in Table 3.

It is difficult to apply the rigorous standards proposed for the assessment of pain[32] to patients who have had major surgery because ability to cooperate is limited. Hence the adoption of the simple indicators used in this study, where the number free from pain in each 4-hour period is proxy for a pain relief score, and opiate consumption in the same period is proxy for a pain score. Any comprehensive review of the quality of postoperative analgesia usually achieved[33] makes depressing reading, and it has long been good practice to treat postoperative pain more aggressively than either 'as required' or '4 hourly' prescription of opiates allows.[34] The use of small doses of intravenous opiates and removal of the time restriction on further doses—subject to adequate monitoring of the response and availability of the opiate antagonist naloxone—have proved advantageous. Where pain relief from local anaesthesia is impossible and patient-controlled administration is inappropriate, an alternative to the traditional approach[35] is attractive. The results of this study demonstrate that a satisfactory degree of analgesia from low-dose ITM persists well into the postoperative period. Four group A patients (31%) required no intramuscular opiate at all after operation, and a further two (15%) needed a single dose, one at 30 hours and the other at 38 hours after the end of surgery. This result compares well with the effect of very much higher doses.[20] The other seven group A patients needed further analgesia 24–28 hours after operation. In four of the 13 group A patients (31%), small doses of papaveretum were given intravenously to enhance the analgesia from ITM during the first 24 hours. The largest number of doses needed was four (total dose 8 mg). The total daily analgesic requirement per head in each of the first three postoperative days is shown in Table 4: between-group differences on days 2 and 3 were not significant.

Table 4. *Per capita* opiate requirements in mg papaveretum daily after operation.

	Group A	Group B
Day 1		
Mean (SD)	1.4 (2.5)	63.2 (24)
Range	0–8	20–110
Day 2		
Mean (SD)	24.6 (21)	29.5 (18)
Range	0–60	10–70
Day 3		
Mean (SD)	9.2 (18)	7.9 (13.6)
Range	0–60	0–45

Clinical respiratory depression was not observed in either group, and other complications had insignificant incidence and were not troublesome to the patients. In particular, vomiting was much less common than others have reported[8] with similar doses in non-abdominal surgery. Catheterisation precluded any assessment of urinary problems that may have resulted from either regimen.

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The acute effects of intravenous isosorbide dinitrate during cardiac surgery

R. S. PARSONS, R. C. WETZEL AND K. MOHANDAS

Summary

The acute effects of intravenous isosorbide dinitrate during open heart surgery were studied in 15 adult patients. Consistent and significant ($p < 0.001$) reductions in pulmonary vascular resistance (25% before, 23% after, cardiopulmonary bypass) and mean pulmonary artery pressure (14% before, 13% after, cardiopulmonary bypass) were observed in the absence of significant changes in cardiac index, mean systemic arterial pressures or right or left atrial filling pressures. These findings indicate that after cardiopulmonary bypass, when right ventricular dysfunction with raised pulmonary vascular resistance may occur, selective reduction of right ventricular afterload with isosorbide dinitrate may prove beneficial.

Key words

Pharmacology; isosorbide dinitrate.
Surgery; cardiac.

Current clinical practice during cardiac surgery lays greater emphasis upon the peri-operative preservation of the functional integrity of the left rather than the right ventricle. However, there is now growing awareness of the role right ventricular dysfunction may play in the limitation of cardiac output following cardiopulmonary bypass (CPB).[1,2] One potent cause of right ventricular dysfunction is the increased afterload caused by pulmonary hypertension or increased pulmonary vascular resistance (PVR), but other causes that result from myocardial ischaemia of the right ventricle are now receiving recognition.[3] Increased afterload may further limit both right ventricular function and the cardiac output in the presence of right ventricular myocardial ischaemic injury.

Conventional doses of currently used systemic vasodilators may, when used to reduce PVR, tend to produce systemic hypotension and reduced coronary artery perfusion pressures.[4] Systemic vasodilators may even reduce cardiac output in patients with increased PVR.[5,6] Oral isosorbide dinitrate (ISDN) has been reported to exert a favourable effect on pulmonary artery pressure and vascular resistance in patients following myocardial infarction and with chronic pulmonary hypertension, without severe systemic side effects.[7,8]

For these reasons we investigated the effects, during the peri-operative period, of bolus intravenous injections of ISDN in patients who underwent open heart surgery, in order to assess whether it would be possible to reduce PVR and

R.S. Parsons, FFARCS, Consultant, R.C. Wetzel,* MD, Honorary Senior Registrar, K. Mohandas, MD, Commonwealth Fellow, The Department of Anaesthetics, The United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, Guy's Hospital, London SE1 9RT.
* Present address: The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA.

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pulmonary artery pressure while adequate systemic arterial pressures and cardiac output were maintained.

Methods

With the approval of the hospital ethical committee, 15 adult patients undergoing open heart surgery were studied after informed consent had been given. The physical characteristics and operative procedures are detailed in Table 1. The patients received a standard premedication with lorazepam 2 mg orally 2 hours prior to arrival in the anaesthetic room, followed after 1 hour by an intramuscular injection of diamorphine 5–7.5 mg and hyoscine 0.2–0.3 mg. Peripheral venous and radial artery cannulae and a triple lumen, flow-directed, thermistor-tipped pulmonary artery flotation catheter were inserted under local anaesthesia. After induction of anaesthesia with diazepam 0.2 mg/kg and fentanyl 50 μg/kg, muscle relaxation was provided by a mixture of pancuronium 6 mg and tubocurarine 10 mg for tracheal intubation and ventilation with 100% oxygen to maintain normocapnia. Prior to the start of CPB the patients received supplementary diazepam 0.1 mg/kg and fentanyl 5–10 μg/kg.

Table 1. Physical characteristics of patients and operative data.

Number	15 (7 M: 8 F)
Age, years (SEM)	56.4 (2.7)
Weight, kg (SEM)	66.2 (3.9)
Operations	
MVR	5
MVR + CABG	1
AVR	2
CABG	6
ASD	1

MVR, mitral valve replacement; CABG, coronary artery bypass graft; AVR, aortic valve replacement; ASD, repair of atrial septal defect.

The haemodynamic measurements included the mean radial artery pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP), mean right atrial pressure (RA) and mean pulmonary capillary wedge pressure (PCWP). The cardiac output was measured in triplicate using the thermodilution technique (IL 801 Cardiac Output Computer). The cardiac index (CI), indexed systemic vascular resistance (SVRI), indexed pulmonary vascular resistance (PVRI) and left and right ventricular stroke work indices (LVSWI, RVSWI) were then calculated. Blood was sampled for calculation of the intrapulmonary shunt (Q_s/Q_t) using the IL282 Co-oximeter.

The response to ISDN was determined prior to the induction of anaesthesia and at various points of relative cardiovascular stability before and after CPB. Haemodynamic measurements were made immediately before, and at 3–5 minutes after, an intravenous bolus of ISDN 0.25–0.3 mg. Analysis of the data before and after ISDN was performed using Student's *t*-test for paired data.

Results

The acute effect of an intravenous bolus of ISDN 0.25–0.3 mg upon the measured variables is shown before (Table 2) and after (Table 3) cardiopulmonary bypass. It can be seen that before

Table 2. Pre-bypass values before and after ISDN, expressed as mean (SEM).

	Before ISDN	After ISDN
MPAP, mmHg	28.0 (6.2)	24.2 (5.7)***
MAP, mmHg	72.5 (1.8)	70.8 (1.8)
HR, beats/minute	74.4 (4.7)	73.9 (4.7)
RA, mmHg	3.8 (0.5)	3.4 (0.6)
PCWP, mmHg	13.9 (2.8)	13.1 (2.7)*
PVRI, dyn seconds/cm^5 sq. m	468.3 (110.6)	352.2 (89.0)***
SVRI, dyn seconds/cm^5 sq. m	2417.7 (113.4)	2263.8 (89.3)*
CI, litres/minute/sq. m	2.34 (0.11)	2.43 (0.1)
RVSWI, g m/beat/sq. m	9.1 (1.8)	8.1 (1.7)*
LVSWI, g m/beat/sq. m	27.5 (3.1)	28.5 (3.1)
Q_s/Q_t, %	21.5 (2.2)	19.0 (2.5)
PVRI/SVRI, %	21.1 (5.5)	16.5 (4.5)**

$n = 19$; * $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$.

Table 3. Post-bypass values before and after ISDN, expressed as mean (SEM).

	Before ISDN	After ISDN
MPAP, mmHg	24.8 (2.5)	21.6 (2.4)***
MAP, mmHg	69.7 (1.9)	69.7 (2.0)
HR, beats/minute	95.2 (3.3)	95.0 (3.4)
RA, mmHg	7.4 (0.6)	7.3 (0.6)
PCWP, mmHg	11.0 (0.7)	10.6 (0.9)
PVRI, dyn seconds/cm^5 sq. m	397.9 (48.0)	308.4 (43.6)***
SVRI, dyn seconds/cm^5 sq. m	1963.9 (111.4)	1964.0 (123.4)
CI, litres/minute/sq. m	2.68 (0.13)	2.71 (0.14)
RVSWI, g m/beat/sq. m	7.5 (1.4)	6.4 (1.6)**
LVSWI, g m/beat/sq. m	23.1 (1.6)	23.6 (1.7)
Q_s/Q_t, %	19.9 (1.6)	18.5 (1.5)
PVRI/SVRI, %	23.3 (3.7)	18.6 (3.3)***

$n = 25$; ** $p < 0.005$; *** $p < 0.001$.

Table 4. Results grouped according to MPAP, values expressed as mean (SEM).

	Before ISDN	After ISDN
MPAP > 25 mmHg (n = 12)		
MPAP, mmHg	51.6 (6.5)	45.7 (6.3)***
PVRI, dyn seconds/cm^5 sq. m	900.3 (113.2)	724.6 (90.3)***
MAP, mmHg	65.9 (2.0)	67.2 (2.3)
SVRI, dyn seconds/cm^5 sq. m	1789.8 (165.2)	1764.8 (151.8)
PVRI/SVRI, %	51.6 (5.4)	42.3 (4.7)***
MPAP < 25 mmHg (n = 32)		
MPAP, mmHg	16.7 (0.8)	14.2 (0.7)***
PVRI, dyn seconds/cm^5 sq. m	251.3 (15.8)	178.3 (13.7)***
MAP, mmHg	72.8 (1.5)	71.3 (1.6)
SVRI, dyn seconds/cm^5 sq. m	2298.7 (90.9)	2216.7 (89.9)
PVRI/SVRI, %	11.3 (0.8)	8.5 (0.8)***

*** $p < 0.001$.

CPB there was a 14% decrease in MPAP with a 25% decrease in PVRI. The SVRI decreased by 6% as did PCWP, but there was no change in MAP. The ratio PVRI/SVRI decreased by 22% and RVSWI by 10%. The decreases in MPAP and PVRI after CPB were similar to the pre-bypass studies (13% and 23%, respectively), but there were no changes in SVRI or in PCWP. The ratio PVRI/SVRI decreased by 20% and RVSWI by 15%. There were no significant changes in HR, RA, CI or in Q_s/Q_t either before or after CPB.

In order to determine whether the effect of ISDN depended upon the pre-existing MPAP, the data were analysed after division into two groups according to MPAP. Table 4 summarises the similarities between patients in whom MPAP exceeded 25 mmHg before each study and those in whom MPAP was less than 25 mmHg. In both groups the percentage changes in MPAP, PVRI and PVRI/SVRI were highly significant ($p < 0.001$), whereas MAP, SVRI and CI remained unchanged in both groups. In addition, the percentage changes in MPAP, PVRI and PVRI/SVRI ratio following ISDN were found to be similar for both groups.

Cardiac dysrhythmias did not occur following ISDN in any patient. Two patients, both of whom underwent mitral valve replacement, required isoprenaline infusion for bradycardia after CPB. No patient in this study required any other sympathomimetic agents.

Discussion

The acute haemodynamic changes which followed a bolus of intravenous isosorbide dinitrate were primarily right-sided. PVRI decreased in all cases, whatever the pre-existing value of MPAP. In addition, the percentage changes in

pulmonary artery pressure and resistance appeared to be unrelated to the level of the pulmonary arterial pressure before ISDN. This is consistent with other findings in patients with primary pulmonary hypertension treated with other vasodilating agents.[5] MAP and SVRI were unchanged in the post-bypass period in our patients, in contrast with a previously reported decrease in MAP following high dose ISDN (up to 10 μg/kg/minute) as the treatment for peri-operative systemic hypertension.[9] The findings in this study may reflect the lower dose of ISDN used and the lack of pre-existing systemic hypertension. Furthermore, ISDN administered in this fashion does not appear to act as a venodilator, as reflected by the maintenance of both RA, PCWP and cardiac output. This observation may also account for the absence of systemic effects such as those reported previously with nitroglycerin.[10,11] Additionally, the reduction in the PVRI/SVRI ratio indicates a predominantly pulmonary vasodilator effect[12] and suggests that low dose intravenous bolus ISDN may act as a selective pulmonary vasodilator.

It is reassuring that, despite a reduction in PVRI, Q_s/Q_t did not increase although pulmonary vasodilators may theoretically interfere with hypoxic pulmonary vasoconstriction and thus increase intrapulmonary shunt. Similar findings have been reported previously with ISDN[8,13] and with nitroglycerin.[14]

The reduction in right ventricular afterload in the apparent absence of systemic effects, suggests that ISDN may have two roles. One role may be the management of pulmonary hypertension and the other may be the treatment of right ventricular dysfunction following cardiac surgery. The occurrence of right ventricular dysfunction is becoming recognised more often and peri-operative causes include embolisation of the right coronary artery (with air, blood clot or atheroma) and ischaemic injury due to the failure of myocardial preservation techniques to protect the right ventricular myocardium.[14,15] Right ventricular failure may become vitally important if it occurs in conjunction with left ventricular failure and may critically limit the cardiac output, even in the presence of left ventricular mechanical assistance.[16] This increasing interest in the causes and importance of right ventricular dysfunction supports our belief, based upon clinical observation, that transient right ventricular dysfunction which presents as dilatation of an abnormally contracting right ventricle, with or without dysrhythmias, is a more common phenomenon than has been generally recognised. The occurrence of an elevated pulmonary vascular resistance, which has been reported following CPB,[14,17] would aggravate this right ventricular dysfunction.

It would seem appropriate to treat moderate right ventricular dysfunction by afterload reduction with an agent which does not produce systemic hypotension or reduce coronary artery perfusion pressures. Based on these results we have successfully used ISDN in the treatment of acute right ventricular dysfunction following CPB. We are further investigating the value of continuous infusions of ISDN for the maintenance of optimal biventricular function in the early post-bypass period.

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Myalgia and biochemical changes following intermittent suxamethonium administration

Effects of alcuronium, lignocaine, midazolam and suxamethonium pretreatments on serum myoglobin, creatinine kinase and myalgia

A. S. LAURENCE

Summary

One hundred gynaecological patients for laparoscopy divided into five groups were studied to determine the effects of a number of pretreatments on serum myoglobin, creatinine kinase and myalgia following intermittent suxamethonium administration. One group acted as controls, while the other groups were given intravenous pretreatments of alcuronium 2 mg, midazolam 0.15 mg/kg, lignocaine 1.5 mg/kg and suxamethonium 7 mg. Serum myoglobin was determined by radio-immunoassay. The mean increases in the control group were 167 μg/litre myoglobin at 20 minutes and 196 IU creatinine kinase at 24 hours; 13 out of 20 patients responded with a marked increase of serum myoglobin at 20 minutes and of creatinine kinase at 24 hours. Only alcuronium pretreatment prevented myoglobin increase at 20 minutes, abolished creatinine kinase increase at 24 hours and reduced 24-hour myalgia. The other pretreatments slightly reduced myoglobin increase at 20 minutes and 24-hour creatinine kinase but did not reduce myalgia. Only one patient in the whole study had markedly elevated serum myoglobin at 24 hours. We conclude that only non-depolarising relaxant pretreatment is effective in the reduction of some of the adverse effects of suxamethonium administration.

Key words

Complications; myalgia, myoglobinaemia.
Neuromuscular relaxants; suxamethonium.

Suxamethonium administration is frequently associated with increases in serum potassium[1] and myoglobin,[2] a later increase of creatinine kinase[3–6] and the occurrence of occasionally severe postoperative myalgia.[7–12] Many attempts have been made in the past to reduce suxamethonium-induced myalgia by means of various pretreatments. These have included a small dose of non-depolarising muscle relaxant,[7] intravenous benzodiazepines,[6,8,9] intravenous lignocaine[10–12] and even a small dose of suxamethonium itself, to at least reduce fasciculations[13] and potassium changes.[14]

One of the difficulties when such a study is undertaken, is that of assessing myalgia in a group of patients with a wide age range and diverse types of operation; large groups of subjects are required to overcome these differences. Patients who present for gynaecological laparoscopy (sterilisation or diagnostic laparoscopy), however, are fit women within a narrow age range, expected to have a procedure lasting less

A.S. Laurence, MB BChir, FFARCS, Lecturer, University Department of Anaesthetics, Beech Hill Road, and Northern General Hospital, Sheffield.
Current address: Royal Preston Hospital, Preston PR2 4HT.

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than half an hour and to be mobilised and discharged home on the first postoperative day. They are thus a suitable population for the study of postoperative suxamethonium myalgia, especially as an intermittent suxamethonium technique can be used because of the short duration of anaesthesia needed. Some reports have suggested that intermittent suxamethonium administration might be more damaging than single-dose use.[3,15] Use of an intermittent suxamethonium technique might therefore emphasise the beneficial effects of any pretreatment given prior to suxamethonium.

This study was designed to investigate the relationship between intra-operative and postoperative myoglobin increase, postoperative myalgia and creatinine kinase levels. Gynaecological laparoscopy patients were studied who had been anaesthetised with an intermittent suxamethonium technique preceded by a number of pretreatments. Radio-immunoassay was used to detect serum myoglobin changes, as in our previous studies.[2,15] Preliminary results of this study have been presented to the Anaesthetic Research Society.[16,17]

Methods

Patients who presented for gynaecological laparoscopy (sterilisation or diagnostic laparoscopy) were studied. They were all ASA grade 1, on pre-operative overnight bedrest and were expected to go home on the day following the procedure. Intramuscular injections were avoided pre-operatively. Local ethical committee approval was obtained and all subjects gave consent to participate in the study. Anaesthesia was administered by the author in a standardised manner throughout the whole of the study.

All patients were given an oral lorazepam premedication. A cannula was sited in a suitable forearm vein on arrival in the anaesthetic room and a pre-induction blood sample was drawn for myoglobin and creatinine kinase. The patient was allocated into one of the trial groups in the following way. Control and alcuronium groups were allocated alternately as each successive patient presented until there were 15 in each group. Then patients were allocated *en bloc* to the midazolam, lignocaine and suxamethonium groups until there were 15 in each group. Finally, the number of subjects was increased by allocating the next available patient to each group in rotation until 20 patients in each of the five groups had completed the study.

The pretreatments given and their doses are listed in Table 1. Most patients in the midazolam group were noted to have slurred speech or disorientation after administration of the pretreatment. One patient in the lignocaine group spontaneously complained that she felt 'odd'. No other adverse effects due to the pretreatments were noted.

Anaesthesia was induced with thiopentone 4 mg/kg followed by suxamethonium 1.2 mg/kg and tracheal intubation. Sixty seconds elapsed between the pretreatment and intubation doses of suxamethonium in the case of the suxamethonium pretreatment. Fasciculations that resulted from suxamethonium administration

Table 1. Pretreatments and group characteristics.

	Control ($n = 20$)	Alcuronium ($n = 20$)	Midazolam ($n = 20$)	Lignocaine ($n = 20$)	Suxamethonium ($n = 20$)
Pretreatment dose and method of administration	—	2 mg, 2–3 minutes before intubation dose	0.15 mg/kg, 2–3 minutes before intubation dose	1.5 mg/kg over 60–90 seconds, 2–3 minutes before intubation dose	7 mg, 60 seconds before intubation dose
Mean age (years)	32.1	31.1	32.2	29.6	32.8
Range	24–41	22–39	24–43	19–43	26–43
Mean weight (kg)	61.1	60.0	64.0	58.0	58.2
Range	50–73	50–85	50–97	50–85	45–83
Fasciculation score (total) (maximum score 80)	40	3‡	34	25*	26*
Total increments of suxamethonium	72	96†	75	83	64

* $p < 0.05$, Mann–Whitney test (compared to control group).
† $p < 0.01$, Mann–Whitney test (compared to control group).
‡ $p < 0.001$, Mann–Whitney test (compared to control group).

were graded on a score of 0 (no fasciculations) to 4 (whole limb movement).

Anaesthesia was maintained with mechanical ventilation of the lungs using 66% nitrous oxide in oxygen supplemented by fentanyl 0.05 mg. Enflurane 0.5% was added to the inspired gases in all but the midazolam group. Increments of suxamethonium 20 mg were given as required when signs of muscle activity returned. Further blood samples for myoglobin and creatinine kinase were drawn from the same cannula at 5, 10 and 20 minutes after the intubation dose of suxamethonium. Laparoscopy, with carbon dioxide for insufflation, proceeded concurrently with the blood sampling. A final sample was drawn at the conclusion of surgery in those few cases where anaesthesia continued for longer than 20 minutes. Postoperative analgesia with sublingual buprenorphine or, if necessary, intramuscular papaveretum, was prescribed. Patients whose operation proceeded to laparotomy were excluded from the study.

All patients were visited between 10:00 and 11:00 hours on the following morning. They were questioned in a standardised and initially non-leading manner and scored for myalgia on a scale of 0 (no pains even on repeat asking) to 5 (spontaneous complaint of myalgia immediately the patient saw the investigator). An attempt was made to exclude pain that resulted from the surgical procedure, by discounting abdominal wall and shoulder tip pains. A final blood sample for myoglobin and creatinine kinase was drawn. Most patients were preparing to go home at this stage. A few patients who were unavailable because they had already left the ward were excluded from the study. One patient whose clinical course was uneventful but whose myoglobin and creatinine kinase changes were found to be grossly abnormal, was excluded from the study. This patient was reported with our preliminary results.[16,17]

Samples were separated and frozen prior to assay in batches. Myoglobin was measured by radio-immunoassay with duplicate determination of samples, in the University Department of Anaesthetics laboratories. A reagent kit made by NMS available through RIA (UK) Ltd, was used. Intra-assay variation is 9.4% and inter-assay variation, 10.5% in our laboratory. Creatinine kinase was measured by a Boerhinger kit based on colorimetric reaction-rate determination in a fast centrifugal analyser in the Department of Clinical Chemistry, Royal Hallamshire Hospital, alongside routine service samples.

Results

The mean values for age and weight were similar for all groups. The characteristics of each group are shown in Table 1, along with the total fasciculation score and total number of increments of suxamethonium needed in the first 20 minutes for each group. The total number of increments was slightly greater in the alcuronium pretreatment group compared to the control group ($p < 0.01$, Mann–Whitney test).

Table 2. Results (standard deviations in parentheses).

	Control	Alcuronium	Midazolam	Lignocaine	Suxamethonium
Myoglobin, μg/litre					
Pre-induction	17.4 (7.0)	18.8 (8.7)	16.7 (5.9)	16.6 (7.5)	18.2 (7.5)
20 minutes	184* (189)	19.6 (7.9)	114* (104)	85.2*‡ (60.9)	87.0*‡ (71.7)
24 hours	32.7 (35.8)	19.5 (9.6)	24.9 (10.3)	23.6 (13.7)	24.0 (15.0)
Creatinine kinase, IU					
Pre-induction	56.5 (26.9)	52.9 (21.9)	52.0 (12.0)	50.1 (16.9)	68.0 (47.0)
20 minutes	57.9 (28.9)	53.1 (21.9)	54.9 (13.3)	51.5 (19.0)	70.0 (50.9)
24 hours	253† (360)	58.6 (24.7)	119† (73.1)	146† (118)	203† (192)
Myalgia, total score	42	22§	52	51	38
Myoglobin–creatinine kinase correlation	0.87	0.45	0.82	0.47	0.82
Myoglobin–creatine kinase regression	1.58	1.59	0.56	0.92	1.91

* $p < 0.001$, † $p < 0.05$, Student's *t*-test (compared to pre-induction values).
‡ $p < 0.05$, Student's *t*-test (compared to control group).
§ $p < 0.05$, Mann–Whitney test (compared to control group).

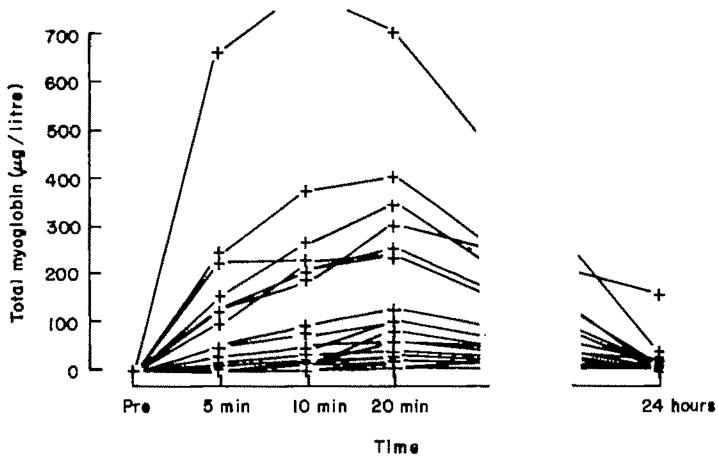

Fig. 1. Serum myoglobin changes: no pretreatment.

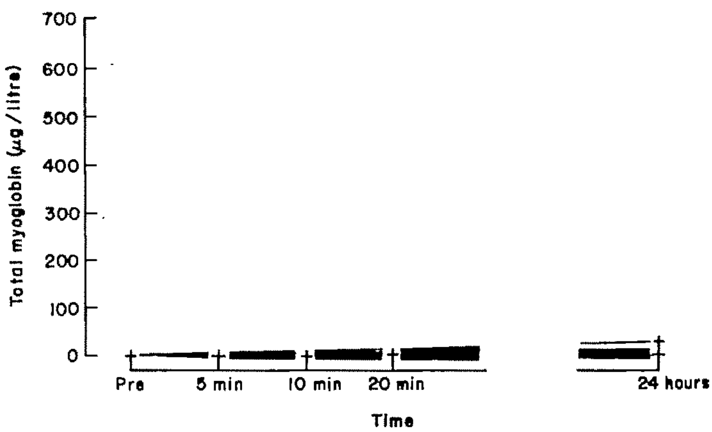

Fig. 2. Serum myoglobin changes: alcuronium pretreatment.

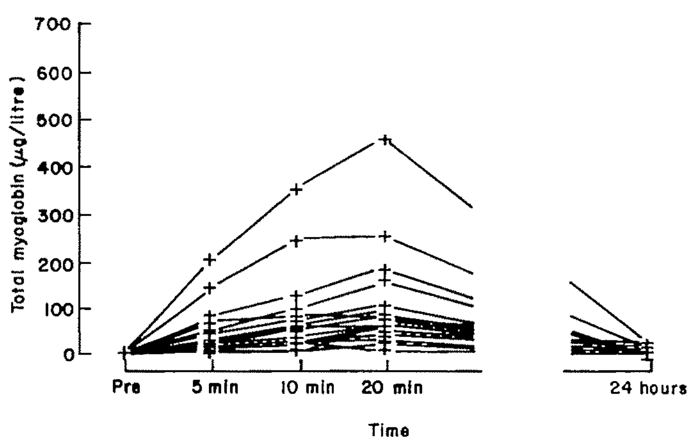

Fig. 3. Serum myoglobin changes: midazolam pretreatment.

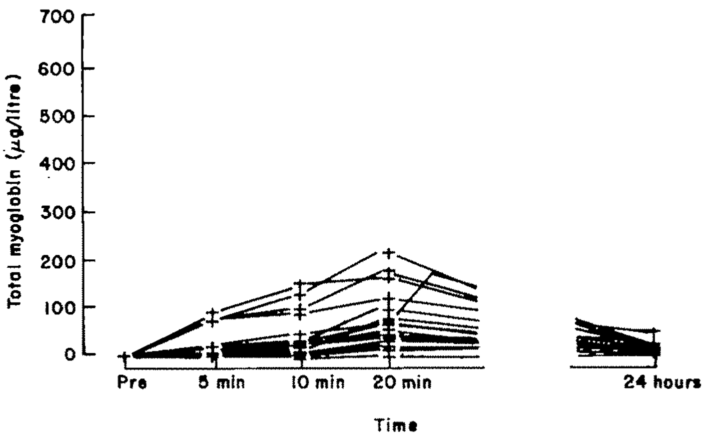

Fig. 4. Serum myoglobin changes: lignocaine pretreatment.

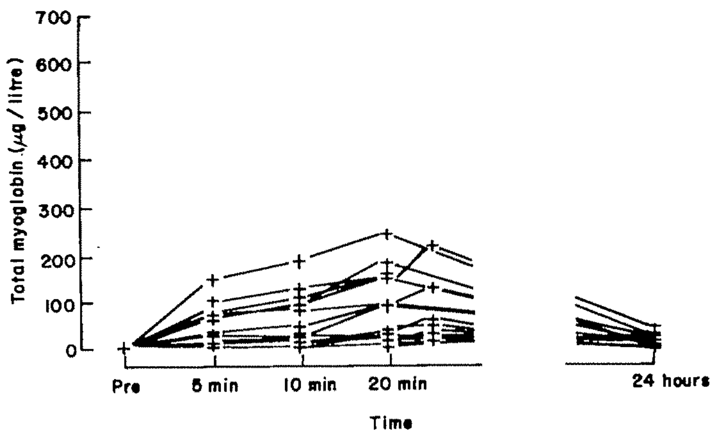

Fig. 5. Serum myoglobin changes: suxamethonium pretreatment.

The results for all groups are summarised in Table 2 and the myoglobin changes presented graphically in Figs 1–5. All pre-induction serum myoglobin and creatinine kinase levels were within the normal ranges for these substances (6–85 μg/litre and 10–170 IU, respectively). The important results in each group are emphasised in the following paragraphs.

Control group

Thirteen out of 20 patients in this group showed an immediate increase in serum myoglobin at 5 minutes and the mean increase for the whole group was 167 μg/litre at 20 minutes. This increase is highly significant compared to either the pre-induction levels or levels in the alcuronium group at comparable times ($p > 0.001$; Student's t-test for the 20-minute values). No intra-operative creatinine kinase increase occurred but creatinine kinase at 24 hours showed a marked increase by a mean value of 196 IU compared to pre-induction levels ($p < 0.05$, t-test). This increase also shows a close correlation with the 20-minute myoglobin rise (correlation coefficient 0.87). There was no significant elevation of 24-hour myoglobin. Total pain score for the whole group was 42. One patient in this group (the only patient in the whole study) showed a markedly elevated serum myoglobin of 175 μg/litre at 24 hours. No cause for this could be found and there was no untoward postoperative myalgia (pain score of 3).

Alcuronium pretreatment group

No patient in this group showed any marked intra-operative myoglobin, postoperative myoglobin or postoperative creatinine kinase increase; the mean values for the group were 0.8 μg/litre of myoglobin at 20 minutes, 0.7 μg/litre at 24 hours and 5.7 IU creatinine kinase. There was still, however, a correlation between the tiny 20-minute myoglobin rise and the small 24-hour creatinine kinase rise (correlation coefficient 0.45). Total pain score for the group was 22, significantly less than for the control group ($p < 0.05$, Mann–Whitney test). The virtual absence of biochemical changes in this group, is highly significant when compared to the control group. The total fasciculation score of 3 for the whole group is also significantly less than for all other groups ($p < 0.001$, Mann–Whitney test). The total number of suxamethonium increments used was greater than in any other group, and was statistically significant compared to the control group ($p < 0.01$, Mann–Whitney test).

Midazolam pretreatment group

The mean myoglobin increase at 20 minutes was 97 μg/litre (13 out of 20 patients showed a rise). Myoglobin increase at 24 hours was 8.2 μg/litre. The mean creatinine kinase increase at 24 hours was 67 IU and, again, shows a good correlation with 20-minute myoglobin. No biochemical parameters were significantly different from the control group. Total fasciculation score, postoperative myalgia score and number of suxamethonium increments were similar to the control group.

Lignocaine pretreatment group

Mean myoglobin increase at 20 minutes was 69 μg/litre ($p < 0.001$ compared to pre-induction levels), less than in the control group, and the difference from the control group at 20 minutes was statistically significant ($p < 0.05$, *t*-test). Postoperative creatinine kinase increase was 96 IU (correlation coefficient 0.47 with 20-minute myoglobin). Myalgia score was similar to that for the control group. Fasciculation score was, however, slightly less than for the control group ($p < 0.05$, Mann–Whitney test).

Suxamethonium pretreatment group

The mean myoglobin increase at 20 minutes was 69 μg/litre ($p < 0.001$), which was also statistically significant compared to the control group ($p < 0.05$, *t*-test), but mean 24-hour creatinine kinase increase was 135 IU (correlation coefficient 0.82). Pain score was comparable to the control group, although fasciculation score was slightly less than for the control group ($p < 0.05$, Mann–Whitney test).

Discussion

This study shows that only alcuronium pretreatment is effective in abolishing increases of myoglobin and creatinine kinase induced by intermittent suxamethonium administration, although the frequency of suxamethonium increments is slightly increased. Additionally, postoperative myalgia is significantly reduced only by alcuronium pretreatment. This is at variance with other workers, who have found that the other pretreatments reduce myalgia.[6,8–12] Our failure to find a reduction of myalgia might be discounted but for the failure of these other pretreatments to prevent myoglobin and creatinine kinase rises as well. It is difficult to explain why these findings seem to differ from those of so many other workers.

The absence of significantly elevated postoperative serum myoglobin levels, despite the presence of postoperative myalgia, is surprising. It suggests that the intra-operative myoglobin increases rapidly but returns towards normal. There was, however, no correlation between myoglobin or creatinine kinase increase, and postoperative myalgia within any group. The presence of postoperative creatinine kinase elevation and its close correlation with intra-operative myoglobin increase, show that postoperative creatinine kinase increase (in the absence of surgically induced muscle damage) and intra-operative myoglobin elevations are both equal indicators of suxamethonium-induced muscle damage. Serum myoglobin measurement would give a useful diagnostic clue to the presence of intra-operative infarction when suxamethonium had been given as part of the anaesthetic technique, as myoglobin elevations are sustained for several days following a myocardial infarction.[18]

The allocation of subjects between the groups was not undertaken in a straightforward way.

This was because it was not certain at the outset of the study that sufficient patients would be available to the author to study all the intended pretreatments. However, the characteristics of patients in each group were similar, all anaesthetics were given by the author in a standardised manner and the surgical laparoscopy technique remained unchanged throughout the study.

Intramuscular injections were avoided preoperatively, so as to minimise any possible muscle damage. It was not thought justified to withhold postoperative intramuscular analgesia, if needed, although sublingual buprenorphine was found to be sufficient in most patients. However, it is probable that small intramuscular injections do not produce any myoglobin increase[18] and it is unlikely that postoperative myoglobin levels were significantly affected by intramuscular analgesic administration. Creatinine kinase levels can, however, be affected by intramuscular injections.[19,20] It might also be argued that intra-operative myoglobin increase might occur due to insertion of the insufflation needle and laparoscope through the abdominal wall. The virtual absence of intra-operative myoglobin and postoperative creatinine kinase increases in the alcuronium pretreatment group, however, shows that this did not occur.

Previous studies have shown that one-third of general surgical patients in control groups given suxamethonium exhibit an increase in serum myoglobin following both single-dose[2] and intermittent administration.[16] In this study two-thirds of patients in the control and unsuccessful pretreatment groups showed a myoglobin increase, and the increase in the control group was greater than found previously in general surgical patients.[16] The most likely explanation is that the mean age of the patients in this study was much less than in the previous studies. Another possible explanation is that there were no male subjects in this study, although there was a majority of females in earlier studies.

The pain due to laparoscopy itself was not assessed using alternative muscle relaxants, such as alcuronium alone. This pain can be considerable.[21] An attempt was made to exclude pain of an obviously surgical origin, such as abdominal and shoulder tip pain, but some of the total pain score in each group might still be due to surgery and not to suxamethonium. However, the statistical ranking test used would still find a significant difference in pain score between groups if such a difference existed. It cannot be hoped to eliminate postoperative surgical pain by simple modifications to anaesthetic techniques.

It is also difficult to explain why the 24-hour creatinine kinase increase was correspondingly greater than the 20-minute myoglobin increase both in the suxamethonium and, to a lesser extent, the lignocaine groups. It is possible that these two agents perhaps delay the effect of any damaging process to muscle. However, the 20-minute myoglobin increase was significantly less in the suxamethonium group than in the control group ($p < 0.05$). The 24-hour creatinine kinase, however, was not significantly reduced. On the basis of some protective effect given by suxamethonium pretreatment, it might be expected that the main (intubating) dose of suxamethonium might have some protective effect against subsequent increments. The fact that intermittent suxamethonium has been found only modestly more damaging than single-dose administration, might support this view.

In conclusion, this study indicates that only alcuronium pretreatment is effective in preventing serum myoglobin and creatinine elevations due to intermittent suxamethonium administration, and in reducing suxamethonium-induced myalgia. Serum myoglobin elevation 20 minutes after suxamethonium administration correlates well with 24-hour creatinine kinase level a appears to yield a good estimation of muscle damage, but not of postoperative myalgia. These findings suggest that the use of pretreatments other than non-depolarising relaxants, is not justified in view of the inconvenience and possible risks associated with their use.

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Carbon dioxide laser bronchoscopy

A review of problems and complications

I. D. CONACHER, M. L. PAES AND G. N. MORRITT

Summary

The records of 20 patients who underwent carbon dioxide laser bronchoscopy were analysed retrospectively. Many of the cases presented with evidence of severe obstruction of the trachea or major bronchi and were regarded as highly at risk from anaesthesia. The majority of problems in the 35 laser sessions related to the use of a rigid bronchoscope for delivering the laser and to the ventilatory difficulties associated with the airway pathology. Invasive arterial monitoring for blood gas analysis and blood pressure measurement proved essential to detect and correct changes of a potentially serious nature. This experience is compared and contrasted with that of others.

Key words

Surgery; bronchoscopy.
Equipment; lasers.

Laser treatment has an established role now in the management of patients with tracheal and other major bronchial lesions.[1,2] The results are usually palliative rather than curative for malignant lesions, but local experience supports the view that such palliation is worth seeking.[3] Many of our 35 patients, who have collectively undergone over 50 laser sessions, have had unpleasant symptoms relieved and achieved prolonged life of improved quality.

Typically, most of these patients presented when seriously ill. The therapy is sufficiently new that, for many, their referral was often a last resort. Such was the condition of their airways that surgery and anaesthesia of any sort may have been life-threatening.

Despite careful pre-operative preparation, many complications occur during laser bronchoscopy. An expectant policy helps to obviate some. The records of the authors' first 20 patients who have undergone carbon dioxide laser bronchoscopy in a period of 2 years, have been reviewed to delineate the complications that have occurred during the learning phase of this relatively new technique.

Patients

Details of the patients are shown in Table 1. Only one[4] had a non-malignant lesion. There were nine males and eleven females with an age range from 37 to 75 years and mean age of 59 years. A quarter were in the seventh decade of life.

The American Society of Anesthesiologists' rating system, modified in 1962, was used to

I.D. Conacher, MRCP, FFARCS, Consultant, M.L. Paes, FFARCS, Consultant Cardiothoracic Anaesthetist, G.N. Morritt, FRCS, Consultant Cardiothoracic Surgeon, Freeman Hospital, High Heaton, Newcastle-upon-Tyne NE7 7DN.

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Table 1. Patient details.

Case number	Sex	Age (years)	Diagnosis	Lesion site	Number of laser sessions	ASA grade
1	M	37	Post-tracheostomy stricture	Mid trachea	11	2
2	F	52	Bronchogenic carcinoma	Right main bronchus	1	4
3	F	73	Bronchogenic carcinoma	Left main bronchus	1	4
4	M	60	Laryngeal carcinoma	Sub-glottis	2	3
5	F	63	Bronchogenic carcinoma	Right main bronchus	1	4
6	M	74	Bronchogenic carcinoma	Left main bronchus	1	3
7	F	75	Bronchogenic carcinoma	Low trachea	1	4
8	M	72	Bronchogenic carcinoma	Carina	1	4
9	F	62	Bronchogenic carcinoma	Low trachea	1	3
10	F	60	Bronchogenic carcinoma	Low trachea	2	3
11	M	58	Bronchogenic carcinoma	Carina	2	3
12	M	54	Bronchogenic carcinoma	Left main bronchus	1	3
13	F	69	Bronchogenic carcinoma	Left main bronchus	1	3
14	M	59	Bronchogenic carcinoma	Right main bronchus	2	3
15	M	74	Bronchogenic carcinoma	Right main bronchus	1	3
16	F	68	Oesophageal carcinoma	Carina	1	4
17	F	59	Bronchogenic carcinoma	Right main bronchus	3	4
18	F	52	Secondary carcinoma, breast	Right main bronchus	1	2
19	M	61	Bronchogenic carcinoma	Right main bronchus	1	2
20	F	59	Bronchogenic carcinoma	Left main bronchus	1	4

Table 2. Factors which affected fitness for operation.

	Number of cases	Percentage of total
Respiratory		
Smokers	17	85
History of bronchitis	3	15
Previous lung surgery	2	10
Stridor	11	55
Grossly abnormal chest X ray	8	40
Abnormal blood gases	3	15
Cardiovascular		
Previous myocardial infarct	3	15
Angina	3	15
Superior vena cava obstruction	4	20
Abnormal electro-cardiogram	7	35
Other therapy		
Chemotherapy and/or radiotherapy	17	85

grade their pre-operative status. However, in some cases, this may not give a true picture of the surgical or anaesthetic risk. The patients' disabilities, including the major airway pathology, were mostly related to a lifetime of cigarette smoking. Stridor and breathlessness were the commonest presenting complaints. Table 2 is a summary of some of the clinical factors which affected their fitness for laser bronchoscopy.

The results of pre-operative lung function tests, the peak expiratory flow rate and the maximal expired volume in 50 seconds ($V_{Emax, 50}$) are shown in Table 3, and give an indication of the severity of the airway obstruction.

Anaesthesia

The duration of bronchoscopy ranged from 20–100 minutes (mean 48 minutes). General anaesthesia was chosen because of the need for a rigid bronchoscope to deliver the carbon dioxide laser and because of the prolonged duration of the procedure. The advantages of local anaesthetic techniques are contrasted to those of general anaesthesia in Table 4. Local anaesthesia has been used for many cases which have undergone therapy with lasers such as the neodymium–yttrium–aluminium–garnet crystal laser (NdYAG) or argon gas laser,[1] that are delivered with a fibreoptic system. The patients received a totally intravenous anaesthetic and volatile agents were deliberately avoided with the exception of case 4, who had a tracheostomy *in situ* to which, on one occasion, a conventional anaesthetic system was attached.

Premedication

Hyoscine or atropine in three and six of the cases, respectively, were administered intra-

Table 3. Pulmonary function tests*.

Case number	Forced expiratory volume, litres	Forced vital capacity, litres	Peak expiratory flow rate, litres/minute	Maximal expired volume $V_{Emax,50}$, litres/minute
1	0.75 (3.70)		39 (490)	
2	0.90 (2.35)	1.40 (3.10)	130 (410)	60 (320)
3	0.85 (1.80)	1.35 (2.80)	201 (368)	43 (319)
4	1.3	2.5		
5	0.85 (2.05)	1.70 (2.90)	100 (365)	28 (234)
6	0.65 (2.15)	1.50 (3.20)	192 (409)	48 (238)
7	0.65 (1.85)	1.40 (2.90)	60 (322)	12 (319)
8	1.3 (2.6)	2.65 (3.85)	96 (420)	48 (210)
9	1.90 (1.85)	2.40 (2.50)	99 (370)	
10	1.10 (1.90)	1.85 (2.50)	150 (350)	
11	1.95 (2.90)	2.40 (3.90)	230 (440)	115 (285)
12	2.80 (3.50)	4.40 (4.70)	396 (480)	158 (266)
13	1.40 (1.70)	2.15 (2.40)		
14	1.35 (2.80)	2.95 (3.85)	216 (425)	36 (245)
15	2.05 (2.45)	2.95 (3.40)	298 (429)	98 (241)
16	1.05 (1.8)	1.65 (2.6)		
17	0.95 (2.20)	1.10 (2.7)	75 (370)	65 (260)
18	1.85 (2.6)	2.55 (3.15)		
19	0.55 (3.15)	2.2 (4.2)		
20	0.55 (2.10)	1.10 (2.55)		

* Normal predicted values for age, sex, weight and height in parentheses.

Table 4. Laser bronchoscopy: local anaesthesia compared with general anaesthesia.

Anaesthesia	Advantages	Disadvantages
Local	No anaesthetist required Simple ventilation	Patient discomfort Disturbed operating field
General	Patient comfort Undisturbed operating field Adequate oxygenation	Anaesthetist required Complex pharmacology Complex ventilation

muscularly to reduce secretions. A benzodiazepine, usually temazepam 30–40 mg, was used as premedication in all but three emergency cases.

Pre-operative preparation

In all patients intravenous (14-G) and radial artery cannulae (20-G) were inserted under local anaesthesia. One patient, whose respiratory workload was significantly diminished by breathing 50% oxygen in helium, continued to breathe this mixture until induction of anaesthesia.

The electrocardiograph (lead I), arterial pressure waveform, systemic blood pressure and heart rate were displayed electronically. Blood gases were analysed every 5–10 minutes during the procedure, and before induction of anaesthesia whilst the patient breathed room air.

Induction

Anaesthesia was induced with an intravenous bolus dose of etomidate 0.2 mg/kg body weight, supplemented in the younger, fitter patients with midazolam 5–10 mg. A dose of opioid was administered at the same time. On nine occasions this was phenoperidine 1–2 mg, on eleven occasions fentanyl 0.1–0.2 mg was used and, latterly, alfentanil 2 mg has been the drug of choice to obtund the reflex responses to tracheal intubation with the rigid bronchoscope. Muscle relaxation at induction in all cases was achieved with atracurium 0.6 mg/kg body weight.

Bronchoscopy

As soon as muscle relaxation was adequate, one of the authors inserted a Negus bronchoscope to assess the airway and to decide on the most

Table 5. Ventilatory techniques for laser bronchoscopy.

Laser	Airway	Motive system	Reference
Argon	Shared	Spontaneous respiration	Hetzel *et al.*[1]
NdYAG	Shared	Spontaneous respiration	Hetzel *et al.*[1]
CO_2	Shared	Ventilating bronchoscope	Snow and Norton[18]
CO_2	Shared	Jet/Venturi	Snow and Norton[18]
NdYAG	Shared	Jet/Venturi	Vourc'h *et al.*[11]
NdYAG	Shared	HFJV	Vourc'h *et al.*[17]
CO_2	Divided	Jet/Venturi	Lee *et al.*[13]
CO_2	Alternated	Jet/Venturi	Conacher *et al.*[4]

HFJV, high frequency jet ventilation.

suitable ventilation technique. Ventilation at this point was, in nearly all cases, maintained with a conventional, manually operated Venturi Sanders system. The Wolf Laser bronchoscope was then inserted and surgery started.

Maintenance

Anaesthesia was maintained with an etomidate infusion initially set to 10 μg/kg/minute and delivered from a syringe pump (Vickers, Treonic). Atracurium was administered as intermittent bolus doses of 0.15 mg/kg when signs of neuromuscular function returned.

Ventilation

Some of the reported ventilation techniques are shown in Table 5. However, improvisation was often necessary when coping with the problems that occurred during anaesthesia. In all cases, except those described below, jet ventilation was used and the bronchoscope was a conduit shared alternately between laser operator and anaesthetist, as described previously.[4]

Case 4 was a man with a laryngeal tumour that extended into his trachea. He had a permanent tracheostomy *in situ* below the site of the operating field. He underwent laser bronchoscopy on two occasions; in both events his tracheostomy tube was changed to a metal one for the procedure. On the first occasion this was connected to a Bain system and ventilation of his lungs was carried out with a Penlon ventilator and, on the second, he was ventilated with an adapted jet system directed down the airway by a bent needle, as reported previously.[5]

Case 5 was a woman with a bronchial carcinoma which blocked her right main bronchus. The left main bronchus was cannulated shortly after induction with a metal tracheal tube of the kind recently described by Hunton and Oswal.[6] A jet ventilator was attached to this and ventilation was applied solely to the left lung throughout the laser session. It was possible to manoeuvre the laser bronchoscope through the rima glottidis alongside the tube to a position above the carina without any apparent trauma to the vocal cords, but the damage so caused has dissuaded the authors from further use of this technique.

It is now our preference to pull the bronchoscope out of the bronchus in which there is tumour, at the time of ventilation, so that the bronchoscope tip is directed down the normal bronchus for a few breaths before the sequence is started again, rather than risk damage to the patient's vocal cords by attempting to divide the airway.

Reversal

At the end of the procedure, neuromuscular blockade was reversed with glycopyrrolate 0.4–0.6 mg and neostigmine 2.5 mg. Patients were discharged to a high-dependency ward for close observation for a further 6 hours until fully awake and able to cough sufficiently well to clear their airways effectively.

Other drugs

Ten patients were given dexamethasone 8 mg on induction of anaesthesia, on the empirical basis that any oedema formation due to airway instrumentation might be reduced. All patients received antibiotics, usually ampicillin and flucloxacillin, as there is a significant morbidity from postoperative chest infections in such patients in the absence of chemoprophylaxis.[1]

Table 6. Operative problems.

	Number of events	Percentage of laser sessions
Blood pressure changes >30% of pre-operative value		
Hypotension	8	23.5
Hypertension	16	47.1
Blood gas changes		
Hypoxaemia <9.0 kPa	9	26.5
<6.0 kPa	4	11.4
Hypercarbia >6.5 kPa	23	67.6
Hypocarbia <4.2 kPa	7	20.6
Acidaemia pH <7.32	18	52.9
Alkalaemia pH >7.46	5	14.7
Electrocardiographic changes		
Bradycardia (<60 beats/minute)	4	11.4
Dysrhythmia	5	14.7

Problems

The problems are summarised in Table 6. The risk of fire is the foremost consideration when lasers are used for the treatment of airway lesions, but no such incident has occurred in the authors' experience. This was attributed to the use of metal instruments for tracheal and bronchial intubation and the avoidance of nitrous oxide, which is known to support combustion.

Blood pressure changes

For the purposes of this review, changes in excess of 30% of the pre-operative, resting systolic levels have been analysed. Decrease in blood pressure of this degree, sometimes to as low as 70 mmHg systolic, was noted on eight occasions; seven occurred on induction of anaesthesia and the blood pressure was restored above normal on intubation. The other episode followed haemorrhage from a tumour. Hypertension commonly occurred. In 11 of the 16 events it was prolonged and unresponsive to extra analgesia or sedation and so was treated with the alpha- and beta-blocking agent, labetalol. Prophylactic intravenous propranolol 2 mg on induction was used on two occasions. Despite this, labetalol was required late during the operative procedure. A dysrhythmia and ST depression were seen only once during hypertensive episodes.

Blood gas analysis

Only three patients presented with abnormal values prior to induction of anaesthesia; in two, oxygen partial pressures were below normal, presumably because of shunting through collapsed lung. In one, the partial pressure of carbon dioxide was decreased. Hypoxaemia occurred during a quarter of the laser sessions. Oxygen tension was below 6 kPa and 60% saturation on four occasions, related to awkward ventilation. On one such occasion, since the bronchoscope was sited in the abnormal bronchus, no ventilation was applied to the contralateral lung and this was corrected by resiting the bronchoscope. On another occasion the lumen of the trachea was so narrow that effective ventilation could be achieved only when the bronchoscope was passed through the obstructing lesion. On two further occasions, haemorrhage from the tumour flooded the narrowed airways and effective ventilation was restored only when haemostasis was secured. Arterial oxygen partial pressures in excess of 40 kPa resulted from the ventilation system, based on a jet technique driven by pipeline oxygen. Better values were achieved by incorporation of an air/oxygen mixer valve (Medishield) in the driving system.

Carbon dioxide retention occurred during nearly 70% of the laser sessions; the highest recorded value was 8.7 kPa. A period of uninterrupted ventilation brought the levels to within the normal range in all cases. Hypocarbia from over-ventilation occurred in 20% of laser sessions.

Acid–base changes reflected the abnormalities in ventilation. The lowest pH recorded was 7.20 and occurred when ventilation and oxygenation were impaired as a result of tumour haemorrhage.

Electrocardiographic changes

Occasional extrasystoles were common. Sinus bradycardia occurred on four occasions, was usually related to intubation and required treatment once. Pulsus bigeminus, with characteristic alternating ventricular extrasystoles, was noted on two occasions, associated with manipulation of the bronchoscope, and resolved spontaneously. A run of ventricular extrasystoles in association with carbon dioxide retention, was

terminated by a bolus injection of lignocaine 1 mg/kg. Severe bradycardia, with bizarre complexes, occurred at the time of one of the hypoxaemic episodes. During a hypertensive episode ST depression was seen and treated as mentioned previously.

Haemorrhage

Bleeding in the confined space of a diseased airway is potentially catastrophic and it occurred on three occasions while vascular tumours were being treated. Haemostasis was achieved by the application of pledgets soaked in adrenaline 1:4000. In two cases, hypoxaemia occurred before haemostasis was secured; in one case, a severe bradycardia followed.

Secretions

Antisialogogues reduced tracheal and bronchial secretion. However, since the bronchoscope does not form a watertight seal at the level of the larynx, there was sometimes spillover of oropharyngeal secretions. A suction catheter passed through the nose into the oropharynx and connected to low suction to drain the retropharyngeal pool of secretions, effectively prevented spillover. A detachable Foregger cuff around a bronchoscope would achieve the same.[7,8]

Smoke and products of vaporization

Ventilation through a common pathway at the same time as carbon dioxide laser vaporization, tends to prevent adequate smoke dispersal. Another danger results from particles of blood that are propelled distally,[9] but this problem was reduced by alternating ventilation with a period of vaporization and suction. Supplementary suction applied to one of the bronchoscope ports has occasionally been necessary.

Serious and late complications

Two cases, numbers 3 and 16 in this series, died within a week of laser therapy. The second of these deaths was due to the progressive advancement of her oesophageal malignancy. A third case (number 10) suffered a stroke 48 hours after the operation.

Case 3. A 73-year-old woman who had previously had chemotherapy and radiotherapy for a bronchogenic tumour of her left lung, presented with distressing dyspnoea and stridor. Three years earlier she had had a myocardial infarct and had since suffered from angina on effort. Her electrocardiograph, besides showing a left bundle branch pattern, confirmed that her atrial fibrillation was at a controlled rate.

Laser surgery was stormy. Torrential haemorrhage from the tumour in the left main bronchus was brought under control with difficulty and not before she had become hypotensive, hypoxic and had developed an extreme bradycardia. Recovery seemed complete after resuscitative drugs and measures and a period of ventilation directed solely to her right lung. However, 5 hours after return to the high dependency unit, she suddenly collapsed and died. She appeared to have sustained a fatal myocardial infarct.

Case 10. A 60-year-old woman with a previous history of myocardial infarction and who had recently had a chemical sympathectomy for peripheral vascular disease, presented with a squamous carcinoma in her lower trachea. She was dyspnoeic at rest and had stridor. The systolic blood pressure was unstable throughout laser surgery. Forty-eight hours after operation and an apparently normal recovery, she sustained a stroke and became aphasic. This recovered over the next week. Ten months later she presented again for laser therapy and her recovery was then uncomplicated.

Since the 20 cases of this series there has only been one further serious complication. A man died at operation and his case report has therefore been appended below.

Case 30. A 60-year-old man, who 3 months earlier had undergone laser vaporization of a bronchogenic tumour which occluded his right main bronchus, presented again for laser therapy. He had recently developed atrial flutter but this had been controlled with verapamil and digoxin. Anaesthesia and laser bronchoscopy were complicated by tachycardia, hypotension and haemorrhage from the tumour site, which was controlled without hypoxaemia. The patient became cyanosed during recovery and underwent bronchoscopy again. Blood clots and pus were aspirated from the left main bronchus. It became impossible to move the chest wall to promote gas exchange even with the bronchoscope tip in the left main bronchus and ventilation applied with a Sanders Venturi system

driven from the oxygen pipeline. The patient sustained an hypoxic cardiac arrest and could not be resuscitated.

Discussion

Fire is the most feared potential problem when lasers are used in an oxygen-enriched environment. However, nearly all reported events of this nature have occurred when combustible materials, such as red rubber and plastic tracheal tubes or dry cottenoids, were in the vicinity of an operating laser.[10] In our cases the operator has occasionally commented on an increased amount of flaring at the operating site in the presence of an elevated inspired oxygen concentration. This may be unavoidable when a ventilator system powered from an oxygen pipeline is used. We have attempted to lower the oxygen concentration using air/oxygen mixer valves but these have not always been successful. They may reduce the driving pressure of the ventilator to such an extent that chest wall movement and tidal ventilation may not be sufficient for effective gas exchange in the presence of the high impedance from lesions that obstruct the trachea or major bronchi.

Vourc'h *et al.*[11] reduced the risk of fire in their large series with NdYAG lasers, by ventilating their patients with an oxygen/nitrogen mixture. By contrast, we use only metal in the airway when the laser is operating and avoid nitrous oxide in the ventilating mix.

The majority of intra-operative problems we have encountered, have been related to the use of rigid instrumentation. Hypertension and cardiac dysrhythmias are both well recognised in association with bronchoscopy, due to laryngeal and tracheal reflex stimulation. The incidence of dysrhythmias in this series was slightly in excess of that quoted for routine diagnostic rigid bronchoscopy when a jet technique of ventilation is employed, but less than that when a ventilating bronchoscope is used.[12] The hypertension can be persistent and difficult to treat. Such reflex responses are probably best suppressed by deep anaesthesia and this may be difficult, given the requirements of having patients awake rapidly and capable of defending their airways after surgery. Alfentanil and labetalol have proved useful for the suppression of hypertensive responses to airway manipulation.

The cardiac dysrhythmias are usually short-lived and often related to movement of the bronchoscope. Nevertheless, both they and the hypertension may forewarn of events of a more serious nature, such as blood gas abnormalities, for which corrective measures are necessary.

The most worrying problems have concerned difficulty in ventilation which has led to carbon dioxide retention or hypoxia. A review of the literature on this aspect of the use of lasers in the trachea and bronchial tree, shows that there are three approaches in vogue to promote gas exchange.[1,2,4,11] These are based on whether the airway is divided, shared or alternated between the anaesthetist and laser operator. In some cases, as in one patient in this series with a tracheostomy, the airway is easily divided with a separate conduit, but in others it is technically more complex and more traumatic for the patient, as in the case described in which the metallic tube was placed in the bronchus contralateral to that of the pathological lesion. Lee *et al.*[13] have described a similar case in which the clear bronchus was cannulated with two catheters, one of which prevented aspiration and the other was used to deliver ventilation.

Pioneers in laser bronchoscopy tended to share the airway,[14] which is useful when the laser is delivered in a separate fibreoptic channel within a rigid bronchoscope.[8,11,15] Ventilation at the same time as the laser was operated, could push contaminated material, blood and particulate matter distally and there were times when smoke extraction was inefficient.[9,11]

The carbon dioxide laser cannot, at present, be delivered fibreoptically so we opted to alternate the use of the shared conduit, namely, the rigid bronchoscope.[4] Smoke evacuation is more efficient and a still operating field can be produced for the operator if the ventilation period is separated from that for laser vaporization. An automatic ventilator has been developed to facilitate the sequential alternation of ventilation and suction.[16]

Motive systems for promoting gas exchange have ranged from spontaneous ventilation techniques, conventional positive pressure generators attached to ventilating bronchoscopes, to the use of high frequency jet ventilation generators.[13,17,18] The jet Venturi technique based on that described by Sanders, is the most favoured, as it has the virtues of simplicity, flexibility and security since there is

usually visible evidence, in the form of chest wall movement with inflation, that gas exchange is occurring.

Complications of laser surgery below the cords include aspiration of blood clot and infected secretions.[10,19] Pneumothoraces, subcutaneous emphysema[10] and pneumopericardium[20] have also been reported as hazards of ventilation techniques in laser cases. Haemorrhage is common and may be fatal.[8]

The experience reported here confirms that the management of patients with tracheobronchial lesions who present for laser therapy, can be technically complex. An expectant attitude should be maintained and the anaesthetic management must be flexible. The majority of problems which confront the anaesthetist are related to the use of rigid instrumentation in the airway of sick patients and are most likely to occur when there is some conflict of interest between operator and anaesthetist. Many patients have little physiological reserve and tolerate insults, particularly respiratory ones, badly. Successful management is attributed to frequent adjustments of ventilation and the cardiovascular system and requires intensive and invasive arterial monitoring.

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CASE REPORT

Piriform fossa perforation during attempted tracheal intubation

D. F. À WENGEN

Summary

Perforation of the piriform fossa is a rare complication of attempted tracheal intubation. The consequences vary from cervical emphysema to respiratory distress, mediastinitis, septic shock, empyema pyopneumothorax and death. The mortality rate due to mediastinitis is over 50%, so early diagnosis and management can improve survival. This case report describes one case and discusses the diagnosis and management of this complication.

Key words

Complications; intubation, tracheal.

Case history

A 62-year-old woman was scheduled for biopsy of her left breast mass. At routine pre-operative assessment she appeared fit and no problems were anticipated with anaesthesia or tracheal intubation. Anaesthesia was induced with thiopentone followed by suxamethonium to facilitate intubation. Ventilation by facemask proved easy but, on laryngoscopy, the vocal cords could not be visualised; only the tip of the epiglottis was visible. Several attempts at blind oral intubation with a Magill rubber oral tube (Rusch) over a stylet were made before the tube was successfully passed into the trachea. Anaesthesia and surgery then proceeded uneventfully. At extubation, however, the patient complained of a sore throat and pain on swallowing. She developed subcutaneous emphysema, initially confined to the neck but spreading rapidly over the thorax and abdomen to the umbilicus. The patient was reluctant to swallow; she preferred instead to spit out saliva.

Perforation of the hypopharynx was suspected and conservative therapy instituted, which comprised restriction of oral intake, antibiotics and steroids. A gastrografin swallow was reported to demonstrate a tracheo-oesophageal fistula. Three days later the oral restriction was discontinued and after one week she was transferred to the University Hospital in Basel. On admission she was apyrexial and complained of slight discomfort on swallowing. There were no signs of infection and indirect laryngoscopy revealed no evidence of hypopharyngeal trauma. A chest radiograph showed widening of the mediastinum (Fig. 2) compared to a previous film (Fig. 1). She requested discharge from hospital as it was Christmas Eve, and was allowed home.

Two weeks later she was re-admitted with a pyrexia of 38–39°C, rigors, generalised weakness and complained of a disturbing feeling of airway compression within her chest. A repeat gastrografin swallow was performed which showed a 2 cm perforation of the right piriform fossa

D.F. à Wengen, MD, Resident, Department of Anaesthesia, University Hospital, CH-4031 Basel, Switzerland.

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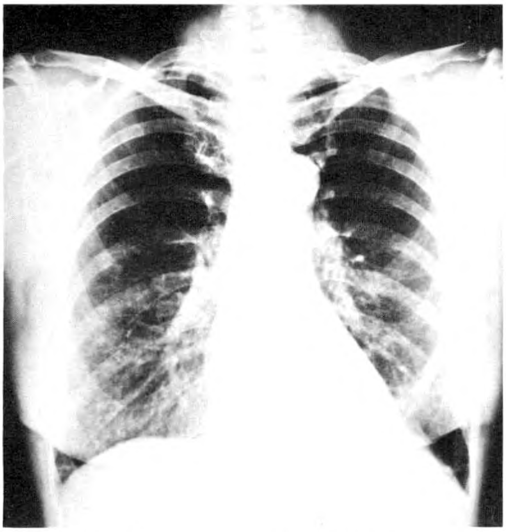

Fig. 1. Chest X ray one year before the event.

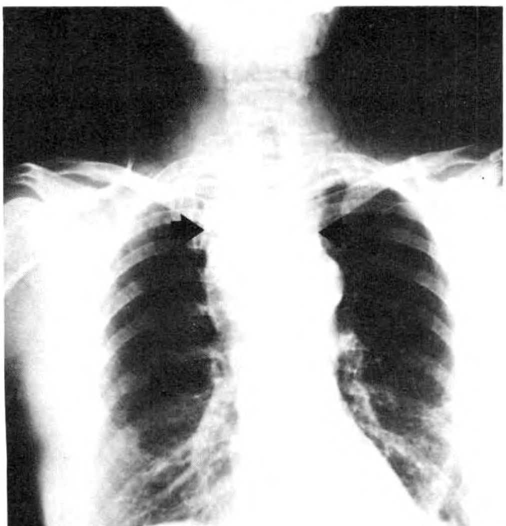

Fig. 2. Chest X ray 7 days after perforation. Substantial broadening of the upper mediastinum in comparison to Fig. 1.

(Fig. 3), which had resulted in a mediastinal abscess the size of a tangerine (Fig. 4). The patient was therefore taken to theatre for drainage of the abscess but, due to inflammation, no site of perforation could be distinguished. A second operation was required for drainage of the abscess and, at a third operation, the perforation was identified and closed. On each of these occasions, intubation with a plastic tube

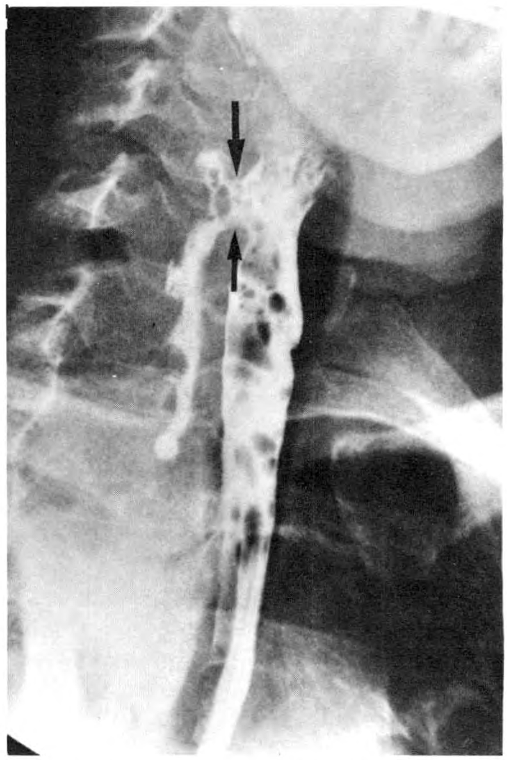

Fig. 3. A 2 cm wide fistula in the right piriform fossa. Gastrografin swallow.

following thiopentone and suxamethonium, was uneventful. Finally, after 63 days, the patient was discharged from hospital.

Discussion

Perforations of the hypopharynx and oesophagus have been described previously.[1–6] Dubost *et al.*[1] reported an incidence of approximately one case per year in the Paris area and described the treatment and outcome of 32 cases reported in the literature. The diagnosis was suspected when a patient complained of dysphagia and neck pain following a difficult intubation. Pseudo-hypersalivation due to discomfort on swallowing, was apparent. In most cases a stylet had been used to facilitate intubation, as in our case. Subcutaneous emphysema over the neck is an early sign, made more prominent if the patient coughs vigorously. Early operation and closure of the perforation may be associated with 100% survival, whilst closure of the perforation delayed for more than 12 hours was associated with a mortality of 56%.[1] In our case, diagnosis was suspected but not confirmed until the 29th day

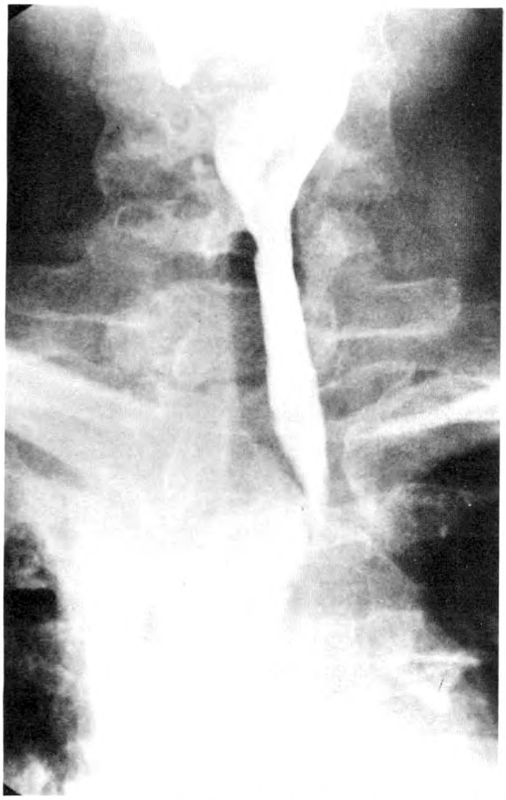

Fig. 4. Mediastinal abscess sitting on the aortic arch secondary to the piriform fossa perforation.

and closure of the defect was performed only after drainage of the mediastinal abscess. The development of mediastinitis may have been delayed by early institution of high dose cefoxitin, or due to partial occlusion of the perforation by a thyroid flap which was found at surgery lying on her cricopharyngeus muscle.

Subcutaneous emphysema and mediastinitis occur frequently following hypopharyngeal or oesophageal perforation. The development of mediastinitis is associated with a high mortality[1] and early closure is therefore desirable. Spontaneous closure of the perforation is unusual and conservative therapy places the patient at greater risk from mediastinitis.

Perforation of the hypopharynx during attempted tracheal intubation may be assumed to occur during efforts at resuscitation under poor conditions.[2,5] However, the majority of reported cases occurred during anaesthesia for planned surgery.[1,3,4] It is hoped that this case report will make anaesthetists more aware of this complication, its association with the use of stylets and the reduction in mortality with early management.

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CASE REPORT

Prolonged paralysis following an infusion of alcuronium in a patient with renal dysfunction

C. L. SMITH, J. M. HUNTER AND R. S. JONES

Summary

The case is described of a patient who underwent artificial ventilation in an intensive therapy unit and received an infusion of alcuronium 10 mg/hour for more than 4 days, in the presence of significant renal (and later, some degree of hepatic) impairment. Prolonged and profound neuromuscular block persisted despite haemodialysis (5 hours on each of 3 days) followed by 72 hours of continuous haemofiltration; it appeared to resolve only after plasma exchange (4 litres). The total period of persistent block, for 9 days after the infusion had been stopped, is thought to be the longest period ever reported after administration of alcuronium. Neuromuscular block was monitored throughout this period using the train-of-four twitch technique. The potentiating effects of concurrent aminoglycoside therapy and hepatic dysfunction on the degree of paralysis are discussed.

Key words

Neuromuscular relaxants; alcuronium, prolonged action.

Prolonged neuromuscular block following the use of a muscle relaxant which depends partly on the kidney for its elimination, has long been known to occur in patients with marked renal impairment. It has been described clinically with gallamine,[1] tubocurarine,[2] pancuronium[3] and in one patient given alcuronium, although after a large dose (42 mg).[4] However, it was predicted in a pharmacokinetic study, that prolonged excretion of more routine doses of alcuronium was also to be expected in the presence of renal failure.[5]

The problem of residual curarisation has diminished with the advent of atracurium and vecuronium, which are almost independent of renal function for excretion. Prolonged curarisation may still occur, however, in the intensive therapy unit (ITU) where infusions of the older muscle relaxants are employed, sometimes for several hours, or even days, in patients with varying degrees of renal dysfunction.

This case report emphasises the need for constant attention when infusions of relaxants are used in patients with renal dysfunction, even when the daily urine volume may appear to be acceptable. Prolonged and profound neuromuscular blockade that lasts for several days, despite both haemodialysis and even plasma

C.L. Smith, MB, ChB, FFARCS, Senior Registrar, J.M. Hunter, MB, ChB, FFARCS, Senior Lecturer, R.S. Jones, MVSc, DrMedVet, FRCVS, DVA, Reader in Veterinary Anaesthesia, General Intensive Therapy Unit, Ward 11Z, 11th Floor, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

Correspondence should be addressed to Dr Jennifer M. Hunter, University Department of Anaesthesia, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX.

exchange, may still occur in such patients if some muscle relaxants are given in large doses by constant infusion.

Case history

A 55-year-old woman was admitted to another hospital having had repeated episodes of haemoptysis over 2 hours. Her haemoglobin level on admission was 5.3 g/dlitre, and blood transfusion was therefore started.

Twelve years previously she had had a carcinoma of the larynx. This had been treated with radiotherapy and she had apparently made a full recovery. Six months prior to her current admission, however, she had developed hoarseness, dysphagia and coughing bouts when eating; there had also been blood streaking in her sputum. Extensive investigations had revealed no abnormality other than distortion of the larynx and pharynx, and barium swallow had shown aspiration into the left lower lobe.

Five hours after admission, she had a further massive haemoptysis, developed profound hypotension and had a respiratory arrest which necessitated tracheal intubation and artificial ventilation. She was resuscitated successfully and the tracheal tube was removed but a few hours later, after she had been admitted to the ITU, tracheal intubation became necessary again and intermittent positive pressure ventilation of the lungs (IPPV) was restarted.

Morphine (2 mg/hour) and alcuronium (10 mg/hour) by infusion were started at this stage and continued for the next 4.5 days. The serum urea and creatinine concentrations had both been elevated (Table 1) on admission to the ITU in the original hospital, and haematuria and proteinuria were present, indicating intrinsic renal pathology.

The adult respiratory distress syndrome (ARDS) developed and inotropic support became necessary after 2 days in the ITU. Treatment with methylprednisolone (2 g daily) was commenced and ceftazidime added to her antibiotic regimen (*Staphylococcus aureus* and *Pseudomonas aeruginosa* had been isolated from tracheal aspirates and were later produced by blood culture).

She was transferred to this ITU 5 days after the cardiorespiratory arrest for further investigation of her renal dysfunction. She was extremely ill

Table 1. Serum urea and electrolyte concentrations and liver function tests at regular stages of the patient's illness, together with blood tobramycin levels (pre, prior to bolus dose of tobramycin 80 mg; post, 30 minutes after bolus dose).

	Sodium (mmol/litre)	Potassium (mmol/litre)	Bicarbonate (mmol/litre)	Urea (mmol/litre)	Creatinine (μmol/litre)
Normal range	130–150	3.6–5.4	20–30	3.0–7.0	60–110
Following cardiorespiratory arrest	138	5.2	—	31.6	486
On admission to ITU	122	4.9	24	41.3	576
After 3 days: prior to haemodialysis	118	4.3	22	53.3	604
After 6 days: prior to haemofiltration	138	5.4	31	26.0	252
After 9 days: prior to plasma exchange	131	4.3	29	29.6	197
After 12 days	137	4.7	26	21.2	197

	Total bilirubin (μmol/litre)	Alanine transaminase (U/litre)	Glutamyl transferase (U/litre)	Alkaline phosphatase (U/litre)	Tobramycin level (mg/litre)
Normal range	2.0–17	7–45	7–45	35–130	pre <2
Following cardiorespiratory arrest	24	26	—	51	—
On admission to ITU	54	29	9	70	—
After 3 days: prior to haemodialysis	62	43	18	85	random 2.2
After 6 days: prior to haemofiltration	87	84	32	123	pre 1.8 post 4.7
After 9 days: prior to plasma exchange	163	212	36	72	pre 1.3 post 5.8
After 12 days	271	220	44	188	pre 2.5 post 5.8

(APACHE score[6] of 24), but impairments of coagulation and liver function were not pronounced.

She was established on IPPV, a pulmonary artery flotation catheter was inserted and cardiovascular stability achieved with dopamine. It was noted that there was apparently no response to twitch or tetanic (100 Hz) stimulation. Review of the relaxant therapy used in the previous ITU showed that she had received a total dose of alcuronium of 1020 mg by continuous infusion over 108 hours, in the presence of a creatinine clearance which never exceeded 3 ml/minute. Consequently, no more relaxant was administered.

Continuous neuromuscular monitoring was started soon after admission using the train-of-four (TOF) twitch technique[7] and was continued for 9 days. Peripheral oedema necessitated the use of subcutaneous needles rather than surface electrodes. A midazolam infusion was started and treatment with tobramycin and pipericillin initiated; tobramycin levels were measured daily. Renal biopsy on the day after transfer showed crescentic glomerular nephritis and treatment with azathioprine and prednisolone was prescribed.

During the first 2 days following transfer to this ITU the patient's condition improved, and inotropic support was withdrawn. However, no return of neuromuscular function was apparent; an electromyograph (Medelec, MS6) was substituted for the mechanical apparatus, and this confirmed the absence of any neuromuscular activity.

Three days after transfer, haemodialysis was started because of rising concentrations of serum urea and creatinine and also in an attempt to clear the remaining alcuronium. Following 5 hours of haemodialysis on each of the next 3 days (i.e. 6 days after the infusion had been stopped), a minimal response to TOF stimulation of the facial nerve with the clinical nerve stimulator could be detected (first twitch barely visible) but there was no response on stimulation of the ulnar nerve. Neostigmine 5 mg was given at this time and all four evoked responses of the TOF returned on stimulation of the ulnar nerve, albeit with marked fade (train-of-four ratio D′/A′ = 10%). This TOF response faded gradually, however, and A′ disappeared 6 hours after administration of neostigmine. Continuous haemofiltration (instead of haemodialysis) was then started in an attempt to hasten alcuronium excretion.

After 72 hours of continuous haemofiltration, and 9 days after the alcuronium infusion had been stopped, the patient began to attempt to open her eyes; post-tetanic facilitation was noted on stimulation of the ulnar nerve but with no response to twitch rates of stimulation. By this time her clinical condition had improved, except for increasing jaundice (Table 1). Haemofiltration was discontinued and a 4-litre plasma exchange was performed in a further attempt to increase the speed of recovery from neuromuscular block. There was rapid recovery of the twitch response over the next 2 hours and no fade of the TOF was present 6 hours later. Full recovery occurred 9 days and 12 hours after the infusion had been stopped. Continuous neuromuscular monitoring was discontinued as no subsequent deterioration in the height of the TOF occurred over a further 6 hours.

Neuromuscular function was checked frequently and remained normal. However, the patient's condition deteriorated, and she died 13 days after transfer. Postmortem examination showed staphylococcal abscesses in the lung fields: the aetiology of her original haemoptysis could not be determined.

Discussion

Muscle relaxants are not as important as sedative drugs in the ITU but they are still used occasionally to assist with artificial ventilation, especially when the patient is first admitted, whilst monitoring lines are inserted or when lung compliance is very poor. Bolus doses of non-depolarising drugs such as pancuronium or alcuronium can be used satisfactorily for this purpose, although prolonged neuromuscular blockade may ensue in patients with renal failure.

It is not unusual to use infusions of non-depolarising muscle relaxants in the ITU; indeed, this may possibly become more common with the advent of atracurium and vecuronium (which are relatively rapidly cleared), although the older agents may still be used because they are cheaper. In the severely ill patient in the ITU, however, deterioration of renal function is common, often as a result of septicaemia. It is not surprising, therefore, that prolonged curarisation may occur with older agents, such as alcuronium, which are excreted predominantly by the kidney. In addi-

tion, septicaemia may cause hepatic dysfunction and it is probable that the deranged liver function tests in this patient (Table 1) were the result of sepsis. Such dysfunction might partly or completely block any alternative hepatic pathway of elimination.

Alcuronium has been used successfully during surgery in patients with renal failure,[8] but pharmacokinetic studies have suggested that the elimination half-life of alcuronium 10 mg is 200 minutes in healthy patients,[9] and that this elimination may be prolonged in renal failure. It is not surprising, therefore, that in this patient, who received over 1000 mg of the drug, it took 9 days for normal neuromuscular function to recover, even when repeated haemodialysis and haemofiltration were used. Despite earlier reports of peritoneal dialysis being used successfully to reverse residual paralysis produced by gallamine 120 mg in a patient with renal tubular necrosis,[10] it would seem that dialysis is of limited benefit after administration of doses of alcuronium of this order of magnitude: total plasma exchange was required in this patient before significant recovery from paralysis occurred.

The prolonged neuromuscular block seen in this patient may have been potentiated by the administration of daily tobramycin to treat concurrent *Pseudomonas aeruginosa* infection. This aminoglycoside is known to potentiate neuromuscular blockade,[11] mainly by a prejunctional effect, and the blood levels of tobramycin were consistently raised in this patient (Table 1). If, however, an aminoglycoside is the only antibiotic to which a *Pseudomonas* organism is sensitive, as was the problem in this patient, it is impractical to stop such a drug purely to enhance recovery of neuromuscular blockade.

The prolonged paralysis experienced by this patient after an infusion of alcuronium given for several days, demonstrates the need for careful monitoring of renal function in the ventilated patient even in the presence of a good urine output. Plasma exchange transfusion appears to be the most effective method of reversing neuromuscular block of this order of magnitude.

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CASE REPORT

Pneumatic tourniquet paralysis following intravenous regional analgesia

U. T. LARSEN AND P. HOMMELGAARD

Summary

A case of pneumatic tourniquet paralysis with permanent damage is presented. The importance of relating the cuff pressure to the cuff used, the arterial blood pressure and the shape of the arm is emphasised.

Key words

Equipment; tourniquets.
Complications; nerve damage.

Upper limb paralysis following the use of a tourniquet to establish a bloodless field, was formerly a well known complication, especially with the use of rubber tubing or elastic bandage. The estimated occurrence of this complication with the use of pneumatic tourniquets is 1 in 5000–8000 operations that require a bloodless field.[1,2]

We describe an upper extremity paralysis with incomplete recovery following intravenous regional analgesia using a double cuff tourniquet.

Case history

An otherwise healthy girl aged 16 years, weight 64 kg, was scheduled for fixation of fractured proximal phalanx of the 5th left finger, which was reduced after 2 weeks of conservative treatment. She was given oral diazepam 10 mg one hour before anaesthesia. A double cuff (each 5 cm wide) pneumatic tourniquet was placed around the upper arm over a felt pad 0.5 cm thick. Venflon® 1.2-mm cannulae were inserted into a dorsal vein of both hands. The sphygmomanometric blood pressure measured on the right arm was 140/80 mmHg.

The left arm was exsanguinated with an Esmarch bandage, after which the proximal half of the double cuff was inflated to 250 mmHg using an automatic tourniquet inflator. Lignocaine 0.5% 40 ml was injected intravenously in the left hand. After 10 minutes, the distal half of the cuff was inflated to 250 mmHg and thereafter the proximal cuff was deflated. The operation was completed in 50 minutes and the cuff was deflated. The patient had no complaints and was discharged from hospital the same day.

The next day the patient noticed weakness in the fingers of the left hand, but she did not contact a physician. On a routine visit to the hospital on the 6th postoperative day, examination revealed paralysis of the left wrist and fingers and weakened flexion of the left elbow. Hypaesthesia and hypalgesia were present on the

U.T. Larsen, MD, Registrar, P. Hommelgaard, MD, Consultant, Department of Anaesthesia, Silkeborg Hospital, DK-8600 Silkeborg, Denmark.
Correspondence should be addressed to Dr P. Hommelgaard please.

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volar side of hand and fingers and the dorsal side of the 1st, 4th and 5th fingers. Biceps, triceps and radialis reflexes were normal. Damage to the radial, ulnar, median and musculocutaneous nerves localised to the upper arm was suspected, and confirmed by electromyography. This revealed total loss of motor units in abductor pollicis brevis (median nerve), abductor digitus minimus (ulnar nerve) and extensor indicis (radial nerve). There was no spontaneous activity in these three muscles. A less pronounced lesion was found in biceps brachii (musculocutaneous nerve). The motor nerve conduction velocities in the forearm were normal.

One month later, no sensory defect was found; however, the motor defects showed little improvement. At a final examination 14 months postoperatively, a slight weakness of the wrist, especially in twist and stir movements, was still present.

When injury in our patient was first detected, the tourniquets and pressure gauges were checked. No faults were found at that time.

Discussion

Paralysis due to pneumatic tourniquets is a rare complication. Only 16 cases have been reported and detailed information is provided only in three publications.[3–5] Direct pressure caused by the pneumatic cuff is regarded as the main cause of nerve lesion[3–6] and experimental findings showed mechanical deformation of the nerve fibres with displacement of the nodes of Ranvier and distortion of the paranodal myelin.[7] Ischaemic injury may also play a part,[8] as the pressure can cause peripheral nerve degeneration. Regeneration time and course are difficult to evaluate, but usually recovery is complete.

In the published cases, the tourniquet time varied from 28 to 160 minutes. It is generally accepted that the compression time should not exceed 2 hours. This limit is based mainly on experimental findings which concern muscle acidosis.[9]

The pressure recommended for a pneumatic cuff applied to the upper arm is either systolic blood pressure +50 mmHg, or 250 mmHg in adults and 200 mmHg in children. These recommendations were followed in our patient. In several of the previously described incidents, there had been faults with the pressure gauge which resulted in application of a much higher pressure than intended.[5–10] This did not seem to be the cause in our patient.

Intravenous regional analgesia is used widely for minor orthopaedic surgery, but few tourniquet injuries have been reported. The use of bupivacaine for intravenous regional analgesia has made it apparent that there can be considerable leakage through the cuff, and this may result in toxic reactions.[11–12] If the recommended pressure is used, leakage is found in 60% of patients, and even with a pressure of 300 mmHg there may be leakage.[13] Congestion of the arm despite the use of recommended pressure, has also been reported.[13]

These complications are most common with the use of narrow double cuffs. With these low-compliance cuffs, cuff pressure is probably not identical to the pressure applied to the arm. Therefore, a cuff pressure much higher than previously recommended may be necessary. Measured arterial occlusion pressure for the cuff used +100 mmHg has been proposed for these cuffs.[13,14] This tendency to increase cuff pressure may be dangerous, if it is not related to the type of pneumatic tourniquet used.

In order to minimise the risk of tourniquet paralysis we recommend that before intravenous regional analgesia, the gauge used should be checked. The arterial occlusion pressure should be determined for the cuff used, and the pressure must not exceed the occlusion pressure +100 mmHg. The tourniquet time must not exceed 2 hours. In obese (>32 cm circumference) or conical upper arms, the double cuff tourniquet should be avoided.

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CASE REPORT

Postoperative complications of dystrophia myotonica

J. K. MOORE AND A. P. MOORE

Summary

A 44-year-old man with known mitral stenosis presented for minor surgery. Anaesthesia was induced with fentanyl, droperidol and etomidate and maintained with nitrous oxide, oxygen and vecuronium. Surgery and anaesthesia were uneventful but the postoperative course was stormy, with respiratory arrest, Haemophilus pneumonia, refractory cardiac dysrhythmias and gastrointestinal atony. A diagnosis of dystrophia myotonica was made after 3 weeks in the intensive care unit, and he spent 6 weeks in hospital. A high index of suspicion for this disease must be maintained and intensive care facilities and monitoring should be available for all procedures.

Key words

Complications; dystrophia myotonica.

Dystrophia myotonica is a rare but serious inherited disorder which may pose substantial problems for the anaesthetist.[1] Peri-operative morbidity and mortality are still appreciable even with appropriate pre-operative evaluation and a planned strategy for each procedure. This paper describes the course and management of a patient with undiagnosed dystrophia myotonica. The case exemplifies the postoperative problems that may be encountered and illustrates the multisystemic nature of the disorder.

Case history

A 44-year-old male who complained of weakness of both legs was referred to an orthopaedic surgeon. No skeletal abnormality was noted but he was obese and mildly hypertensive and was therefore referred for medical assessment. Mitral stenosis was diagnosed by a cardiologist and confirmed by ultrasound echocardiography. He was commenced on therapy with digoxin 0.25 mg, frusemide 40 mg and potassium chloride 600 mg daily. Mitral valve replacement was recommended, prior to which a dental clearance was performed under general anaesthesia with Althesin, fentanyl and atracurium. His lungs were ventilated with nitrous oxide, oxygen and enflurane and the half-hour procedure was uneventful. Atropine and neostigmine were not required for the reversal of muscle relaxation and he was discharged from hospital after 1 week. Two months later a surgical opinion was sought for the presence of a breast lump and he was admitted for a biopsy with consent for mastectomy if necessary. Pre-operatively he had a history of cholecystectomy 7 years previously, the recent dental clearance and bilateral leg weakness for 1 year. He smoked 10 cigarettes a day and always had a cough with green sputum. He admitted to weight loss but no other gastrointestinal symptoms were elicited. Examination revealed an obese man in atrial fibrillation. The apex rate was 80 beats/minute, systemic arterial

J.K. Moore, MB, ChB, FFARCS, Senior Registrar in Anaesthesia, Royal Infirmary, Glasgow G31 2ER, A.P. Moore, MB, ChB, MRCP, Registrar in Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF.

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blood pressure was 125/70 mmHg, the heart was enlarged and a diastolic murmur was audible. Auscultation of the lungs revealed scattered crepitations and rhonchi. He was receiving digoxin, frusemide and potassium chloride. Pre-operative chest X ray showed mild left atrial enlargement and prominent pulmonary arteries, and serum electrolytes were normal.

On the day of his operation he received lorazepam 2.5 mg for premedication. Anaesthesia was induced with fentanyl 250 μg, droperidol 5 mg and etomidate 20 mg. Vecuronium 8 mg was used to provide muscle relaxation and his trachea was intubated and the lungs ventilated with nitrous oxide and oxygen. Biopsy and frozen section of the breast lump took 60 minutes, and one increment of vecuronium 2 mg was required to maintain adequate muscle relaxation. Throughout the procedure his heart rate remained between 70 and 90 beats/minute in atrial fibrillation, and his blood pressure was stable at 110–125 mmHg systolic measured at 5-minute intervals using a Dinamap recorder. Histology of the frozen section revealed benign gynaecomastia and the operation was terminated. Residual neuromuscular blockade was reversed with glycopyrronium 0.4 mg and neostigmine 2.5 mg and his trachea was extubated in theatre, when he was reported to be breathing well. He was transferred to the recovery ward where he had a respiratory arrest 30 minutes later. An electrocardiogram revealed episodes of unifocal ventricular ectopic beats interspersed with bursts of ventricular tachycardia. A diagnosis of pulmonary oedema was made on the basis of an emergency chest X ray, his trachea was re-intubated without the use of relaxants and he was transferred to the intensive therapy unit.

His cardiovascular system remained extremely unstable for the next 48 hours, during which period he was treated with disopyramide, dopamine and lignocaine infusions. He developed varying conduction defects and dysrhythmias that included fast atrial fibrillation, right bundle branch block, ventricular tachycardia and one episode of ventricular fibrillation which was terminated by electrical defibrillation. He was finally stabilised on a lignocaine infusion and the Althesin infusion rate was reduced in order to assess his neurological state. He spontaneously moved all four limbs but did not open his eyes. Pulmonary gas exchange remained poor, with increasing hypoxia, and $Pa\text{O}_2$ decreased to 49 mmHg with $Pa\text{CO}_2$ 37 mmHg despite ventilation with 100% oxygen and 5 cm H_2O of positive end expiratory pressure. A *Haemophilus pneumoniae* respiratory infection was diagnosed and appropriate antibiotics started. He was commenced on parenteral nutrition on the third postoperative day. Pulmonary function had improved sufficiently to permit tracheal extubation by the sixth postoperative day. However, his condition rapidly deteriorated and he required re-intubation, for which he was given Althesin 1.5 ml and suxamethonium 75 mg. Over the following week he developed consolidation at the left base and right mid-zone and he remained extremely drowsy, although he received no sedation. Because he was unable to cough and had persistent problems with retained secretions, he required ventilation for 3 weeks before attempts at weaning him from ventilatory support were successful.

It was not until this point that he was diagnosed as suffering from dystrophia myotonica. Clinical examination demonstrated the classical features of bilateral ptosis, facial weakness and frontal balding with wasting of temporalis, sternomastoids and masseters. There was testicular atrophy and he had presented with gynaecomastia. He had difficulty in swallowing his saliva and percussion myotonia could be elicited in the thenar eminence.

The re-introduction of enteral feeding was troublesome and he continued to require parenteral nutrition with infusion of insulin to control hyperglycaemia. He was commenced on distigmine bromide 0.5 mg twice daily intramuscularly and his gastrointestinal function gradually improved; this enabled parenteral nutrition to be stopped on the twenty-fifth postoperative day. He was finally discharged home some 6 weeks after his operation, at which time he had a hoarse voice, slurred speech and a shuffling gait. He was later reviewed by the department of neurology who demonstrated the characteristic electromyographic picture of dystrophia myotonica, but he was reluctant to undergo any further investigations or to submit his family to scrutiny.

One year later he underwent mitral valve replacement. Pre-operative assessment demonstrated a severe restrictive ventilatory defect (VC 1.8, FRC 1.56, TLC 2.81 litres) but no airway

obstruction. The left atrium was enlarged, left ventricular function was normal and the gradient across the mitral valve was 9 mmHg. Anaesthesia was induced with morphine 25 mg and thiopentone given incrementally to a total of 150 mg. Vecuronium (increments to 7 mg) was used to provide neuromuscular relaxation. On tracheal intubation he was found to have a tracheal stenosis which would admit only a 7.5 mm (ID) tracheal tube. Anaesthesia was maintained with nitrous oxide and halothane in oxygen, supplemented by morphine and midazolam as required. Anaesthesia and surgery were uneventful and postoperatively he was ventilated electively. He had difficulty in clearing his secretions and remained intubated for 1 week, requiring intermittent ventilatory assistance. He was discharged from hospital 16 days after surgery, less dyspnoeic than pre-operatively.

Discussion

Dystrophia myotonica was described by Steinert[2] in 1909. It is inherited as an autosomal dominant with variable expression. Clinical abnormalities suggest a diffuse cell membrane defect and this may involve the sodium–potassium pump or be a primary defect in potassium permeability.[3] There are skeletal and smooth-muscle abnormalities, ocular, cardiac, gastro-intestinal and endocrine problems and mental and personality changes. It may therefore present formidable problems to the anaesthetist in the peri-operative period.[4] Onset is between the ages of 20 and 40 and myotonic symptoms usually precede weakness and muscle atrophy, although the major complaint is of weakness of the distal or facial muscles. Death is usual in middle age, from respiratory failure, bronchopneumonia[5] or cardiovascular abnormalities that progress to complete heart block.[6] Death may be sudden or associated with anaesthesia.

Respiratory abnormalities are of particular concern to the anaesthetist. Problems may arise because of the deterioration in pulmonary function. The picture is one of chronic alveolar hypoventilation[5,7] with respiratory muscle weakness and carbon dioxide retention.[8] The severity of the derangement is often unsuspected clinically. Vital capacity and (particularly) expiratory reserve volume may be reduced and maximal expiratory pressure may be only 25% of normal.[5] There is a decreased sensitivity to carbon dioxide, and a primary nervous system component has been postulated as these patients demonstrate excessive somnolence, disproportionate to their mild elevation in $Pa\text{CO}_2$.[4] Weakness of pharyngeal and oesophageal muscles causes abnormal swallowing, and pulmonary aspiration has been demonstrated in the majority of patients.[4]

Cardiac dysrhythmias and conduction defects are common and the patient may develop a cardiomyopathy. An increase in the PR interval is the most frequent abnormality and this is unresponsive to atropine.[4] Conduction block may be aggravated by anaesthesia and surgical stimulation. Pacemakers have been advocated in symptomatic patients and in asymptomatic patients with severe and diffuse lesions,[6] and this should be considered pre-operatively.

Smooth muscle involvement is not as well recognised as skeletal and cardiac muscle involvement and the true incidence is unknown. All organs of the gastrointestinal tract, from the pharynx to the anal sphincters, may be affected and gastrointestinal dysfunction may be the presenting feature of the illness. Jejunal manometry, recently found to be more sensitive in this regard than radiographic studies, has shown a very high incidence of abnormal intestinal motility in patients with dystrophia myotonica.[9] Pentagastrin and edrophonium injections have been shown to increase gastrointestinal motility.[10]

A variety of endocrine and metabolic abnormalities occur. Eighty percent of males have testicular atrophy and females commonly have ovarian dysfunction and fibrosis. Both sexes may have a decreased metabolic rate but thyroid function remains normal. Glucose tolerance is abnormal[11] with delayed utilisation of glucose and a slow return to normoglycaemia after a glucose load. This may progress to frank diabetes mellitus. Patients are resistant to endogenous insulin but respond normally to exogenous insulin,[4] which suggests that they secrete an insulin antagonist.[12] There is excessive catabolism of immunoglobulin G, which often results in low serum levels and increased susceptibility to infection.[13]

Myotonia is a persistent muscle contraction which can be elicited by mechanical or electrical stimulation of the muscle. Classically the patient is unable to open a tightly clenched fist, or percussion of the thenar eminence produces a

contraction and bunching of the muscle. On needle insertion, electromyography reveals high frequency trains of action potentials whose frequency and amplitude wax and wane, producing a characteristic 'dive-bomber' sound. These features are seen in all of the myotonic disorders but, in dystrophia myotonica, there may also be myopathic changes with action potentials during voluntary contraction which are shorter, of smaller amplitude and more frequent than normal, and a normal interference pattern on maximal effort.[14]

Most anaesthetic and relaxant drugs have been stated to be dangerous in patients with dystrophia myotonica.[12] There is increased susceptibility to central nervous sytem depressants including the barbiturates, opiates and volatile anaesthetic agents. Halothane may be further contraindicated because of its myocardial effects and propensity to cause postoperative shivering which may induce myotonia.[4]

The production of relaxation during anaesthesia and surgery may be difficult, as a myotonic response may be elicited by surgical stimulation and diathermy. Nerve blocks and muscle relaxants may not prevent myotonia, as the defect is at the cell membrane. The non-depolarising muscle relaxants elicit a normal response, but neostigmine may induce myotonia in some patients. The response to suxamethonium is unpredictable, and it can precipitate widespread myotonia that makes ventilation difficult or impossible, although over half of patients may respond normally.[4] Suxamethonium may also elevate serum potassium which aggravates myotonia in its own right.[15] Althesin has been reported to prevent percussion myotonia without affecting the electromyogram, which suggests an intracellular effect.[16] The use of intravenous regional anaesthesia with lignocaine has been advocated for extremity surgery,[4] as local infiltration of the affected muscles is effective in reducing spasm.

The intra-operative management of dystrophia myotonica in patients known to suffer from this condition, has been reviewed extensively in the literature,[1,4,12,15–18] but we could find no reports specifically of the complications that may result from anaesthesia in patients with undiagnosed dystrophia myotonica. This case history illustrates the prolonged postoperative complications that may arise. There were no problems intra-operatively and anaesthesia was uneventful. This may reflect the cardiac stability of etomidate and vecuronium. Myotonia was not precipitated by surgical stimulation, by the administration of neostigmine in theatre or by the later administration of suxamethonium, although it was possible to demonstrate marked percussion myotonia postoperatively. This illustrates that the balance between myotonia and weakness may vary between muscle groups in the same patient so that pre-operative assessment using peripheral muscles may be misleading. Complications appeared in the postoperative period and demonstrated clearly the widespread nature of the disease. Undoubtedly the underlying disease was the main cause of his persistent postoperative respiratory problems, with severe pulmonary sepsis, aspiration of saliva, inability to cough and sputum retention and it was responsible for his excessive drowsiness and gut atony. It may also be implicated in his cardiac conduction defects, although he had proven mitral stenosis. However, the intraoperative use of fentanyl and droperidol may have contributed to respiratory depression in the early postoperative period; with foreknowledge of his disease, these drugs and the subsequent use of neostigmine and suxamethonium might have been avoided.

It is interesting that he had undergone uneventful surgery and anaesthesia 2 months previously with no intra- or postoperative complications. On that occasion he received Althesin and atracurium. Atracurium has been advocated in dystrophia myotonica[19] both in its own right and because neostigmine can be avoided.[20] Anaesthesia for his cardiac surgery was uneventful, even though drugs with theoretical disadvantages had to be used: no drug is completely safe in this condition. The most important factor is anticipation of the potential problems.

In a patient who is known to have dystrophia myotonica, pre-operative evaluation should include detailed assessment of cardiovascular status, including 24-hour electrocardiogram monitoring[21] and pulmonary function tests. The anaesthetist may then select the best approach for the surgical procedure planned. Patients still present for surgery with undiagnosed dystrophia myotonica because of the variable expression of the disease and its low incidence in the general population. The diagnosis is made primarily on clinical grounds and so main-

tenance of a high index of suspicion is important, particularly in patients with diabetes mellitus, pre-senile cataracts or musculoskeletal abnormalities. In view of the diverse and potentially life-threatening complications which may occur after even minor procedures, these patients should all be monitored postoperatively in a high dependency or intensive therapy unit even if the course of anaesthesia appears to have been uneventful. Neuromuscular disorders should be considered in patients with an unduly stormy postoperative course.

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Anaesthesia, 1987, Volume 42, pages 534–535

CASE REPORT

The use of bronchial stents in the management of bronchomalacia

J. M. GODDARD AND P. D. BOOKER

Summary

A case is described in which the use of a bronchial stent proved very useful in the management of an infant with severe air trapping secondary to bronchomalacia.

Key words

Lung; bronchus.

Case history

A term male infant with tetralogy of Fallot and absent pulmonary valve, was transferred at 2 weeks of age for surgical assessment. He had been delivered by forceps, weighed 3.3 kg and had Apgar scores of 2 at 1 minute and 5 at 5 minutes. Ventilation of the lungs through a tracheal tube was commenced at birth for persistent cyanosis and it had proved impossible to withdraw this support. A chest X ray on the first day of life had shown very large pulmonary arteries and the heart displaced into the right chest due to air trapping; cardiac catheterisation on day 6 had confirmed the diagnosis of tetralogy of Fallot and absent pulmonary valve.

A chest X ray showed the tracheal tube to be at the level of the carina; the mediastinum was displaced to the right by a hyperinflated left lung. The tracheal tube was changed several hours later because of difficulties with ventilation, and positioned with the tip in the mid-trachea.

Echocardiography showed a ventricular septal defect of 12 mm diameter and the aorta overriding 60%; the right pulmonary artery was 11 mm in diameter and the left pulmonary artery 12 mm in diameter. A patch closure of the ventricular septal defect was performed on the following day with the use of cardiopulmonary bypass and circulatory arrest, an aortic valve homograft was inserted in the right ventricular outflow tract and the left pulmonary artery was plicated. The position of the tracheal tube was not altered during this procedure.

Gross shift of the mediastinum to the right occurred in the immediate postoperative period, associated with hypotension. Bronchoscopy showed the right main bronchus to collapse in the absence of positive pressure; the left main bronchus was a slit-like aperture flattened anteriorly. The patient was stabilised using a rigid Stortz suction catheter as a stent in the left main bronchus, and the tracheal tube in the mid-trachea. Removal of the suction catheter caused rapid deterioration in the patient's condition and it was therefore repositioned in the left main bronchus. Arterial $P\text{CO}_2$ was 4.7 kPa and $P\text{O}_2$ 6.6 kPa, with $F\text{IO}_2$ 0.7. Echocardiography with saline injection showed a small right to left shunt through the foramen ovale.

Five days later the chest X ray showed less pronounced hyperinflation of the left lung and

J.M. Goddard, MRCP, FFARCS, Registrar, P.D. Booker, MB, BS, FFARCS, Consultant, Department of Anaesthetics, Royal Liverpool Children's Hospital, Myrtle Street, Liverpool L7 7DG.

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the bronchial suction catheter was again removed. A left-sided pneumothorax developed within several hours and required insertion of a chest drain; this bubbled freely for 4 days, at which stage a more sophisticated stent was inserted into the left main bronchus. This was fashioned from a short length of Portex tracheal tube which was attached to a stiff Stortz suction catheter using superglue. Suction was subsequently applied to the chest drain. When the drain stopped bubbling, first the bronchial stent and later the chest drain were removed uneventfully.

Repeat bronchoscopy, 4 weeks after operation, showed some improvement in the appearance of both main bronchi. The patient was weaned onto spontaneous ventilation with continuous positive airway pressure (CPAP) and his trachea extubated 10 days later. However, within 24 hours he required re-intubation for respiratory distress; a tracheostomy was performed and he was re-established on CPAP before he was transferred back to the referring hospital for long-term ventilatory support.

Discussion

Bronchomalacia is increasingly recognised as a cause of severe respiratory distress in infancy. Patients have tended to be managed medically although in 1963, Pontius[1] described successful surgery on several infants without recourse to pneumonectomy. Two patients with a patent ductus arteriosus and one with a ventricular septal defect had pulmonary arteriopexies; a further patient had surgery to an aberrant left pulmonary artery. Recently there was a report of successful segmental bronchial resection in an infant of 9 months with bronchomalacia secondary to ventilation for respiratory distress syndrome.[2]

Tetralogy of Fallot and absent pulmonary valve are associated with aneurysmal dilatation of the main pulmonary artery and its first-order branches, which frequently results in tracheobronchial obstruction and severe respiratory distress. Several reports now suggest encouraging results with early surgical treatment of the intracardiac defects combined with pulmonary arteriopexy to relieve the tracheobronchial compression. In 1981 there was a report of a good result achieved by closure of the ventricular septal defect and plication of the right pulmonary artery in the neonatal period.[3] Of two patients reported in 1983, a 4-month infant did well after reconstruction of the pulmonary arteries and closure of the ventricular septal defect, while the second infant died as a result of faulty aneurysmorraphy design.[4] This case report also mentions four further infants in an addendum, and three of these did well after similar surgery. A 2-month child has also been described who underwent closure of the ventricular septal defect, widening of the right ventricular outflow tract and plication of right and left pulmonary arteries.[5] Two staged thoracotomies were performed in the subsequent 2 weeks with further plication of the right and left pulmonary arteries, with a successful result.

These reports indicate realistic surgical options in small infants with bronchomalacia secondary to a number of causes, particularly aneurysmal dilatation of the pulmonary arteries. In the peri-operative period the lungs of these babies can be particularly difficult to ventilate effectively. Air trapping behind a collapsing bronchus is often a troublesome problem which predisposes to the development of a pneumothorax or mediastinal shift. The use of a bronchial stent is, in our experience, a helpful addition in the management of this problem.

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CASE REPORT

Tracheopathia osteochondroplastica

A cause of unexpected difficulty in tracheal intubation

D. C. SMITH, R. PILLAI AND C. E. GILLBE

Summary

A 60-year-old man presented for aortocoronary saphenous vein grafting; tracheal intubation was found to be difficult before surgery. Bronchoscopy at the time suggested tracheal carcinoma, but subsequent biopsy of the trachea demonstrated tracheopathia osteochondroplastica. The condition is described and its implications for anaesthetists are discussed.

Key words

Anaesthesia; thoracic,
Intubation, tracheal; complications.

Tracheopathia osteochondroplastica (TPO) is a benign dysplasia of the trachea and large bronchi, characterised by calcifying cartilaginous outgrowths into the tracheal lumen. Patients remain asymptomatic for many years until they present with dyspnoea, haemoptysis or a dry cough late in the course of the disease. We report a case of TPO which caused difficulty at tracheal intubation; this has been reported only once before.

Case history

A 64-year-old man of Polish origin presented with grade 3 exertional dyspnoea and a one-year history of anginal pain of progressive severity in spite of optimal treatment with calcium antagonists, nitrates and beta-blockers. There was a history of hypertension of 7 years' duration, and of tobacco consumption of 3–4 ounces per week for 50 years. He had complained of a dry winter cough for several years, ascribed to smoking and mild chronic obstructive pulmonary disease. The only major finding in the previous medical history, was treatment with radio-iodine for thyrotoxicosis in 1945. There was nothing remarkable in the social or family history other than periods of detention in the USSR and Germany in the 1940s. Physical examination was entirely normal.

Coronary arteriography demonstrated severe stenosis of the left main stem vessel with intermediate and distal lesions of the left main circumflex and the lateral circumflex arteries. There was moderate long stenosis of the dominant right coronary artery. Left ventricular angiography demonstrated normal left ventricular function. Increased longevity, as well as symptomatic relief, is reported to follow surgical correction of left main stem stenosis;[1] therefore, this option was discussed with, and accepted, by the patient.

The results of pre-operative investigations were normal, apart from the (retrospective)

D.C. Smith, BMed Sci, BM, BS, FFARCS, Registrar, R. Pillai, MB, BS, FRCS, Senior Surgical Registrar, C.E. Gillbe, MB, ChB, FFARCS, Consultant, Brompton Hospital, Fulham Road, London SW3 6HP.
Correspondence should be addressed to Dr C.E. Gillbe please.

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Fig. 1. Cincinnati view X ray to show stenosing lesion of the trachea.

detection on the chest X ray, of a stenosing lesion of the trachea. A subsequent Cincinnati view of the trachea is illustrated in Fig. 1.

Induction of anaesthesia was carried out with fentanyl, pancuronium and thiopentone following medication with papaveretum, hyoscine and a beta-blocker. At laryngoscopy, considerable difficulty was experienced in passing a 9-mm tracheal tube beyond the larynx. Rigid bronchoscopy was performed and the tracheal wall was found to be harder than normal, partly calcified, and bled readily on contact. The trachea was irregularly narrowed; the appearance suggested carcinoma of the trachea. It was decided that surgery should proceed as scheduled and, since heparinisation was required, biopsies were not taken of the trachea at this time. The trachea was intubated with an 8-mm internal diameter tube with the proximal end of the cuff placed just through the cords. Further advancement of this tube caused obstruction to the airway and even in the best position, only a size 10 suction catheter could be advanced freely down the trachea. Surgery proceeded uneventfully and anaesthesia was conducted so that extubation could be accomplished at the end of the procedure, since it was judged that continuing tracheal intubation represented a considerable hazard to the patient.

On the first postoperative day the patient was noted to have a productive cough with some dyspnoea at rest. Sputum was sent for culture and cytology. Physiotherapy and appropriate antibiotics were commenced. The chest infection resolved over the next 7 days, during which time sputum cytology was reported as normal. Fourteen days postoperatively the patient remained stridulous with mild dyspnoea at rest.

Bronchoscopy was repeated under general anaesthesia and the cords and larynx were found to be normal but, 3.5 cm distal to the cords, the tracheal lumen was reduced to a slit. Here the tracheal wall was hard, bled readily on contact and was reported by the surgeon as being almost certainly neoplastic. Biopsy specimens were taken and reported to show dysplastic mucosa with no evidence of malignancy. Tracheoscopy under general anaesthesia 7 days later, when the patient's stridor was resolving, again demonstrated a normal larynx but with irregular narrowing of the distal tracheal lumen produced by hard masses projecting from the anterior and lateral walls. Biopsies were repeated and demonstrated irregular fragments of cartilage and bone situated in the mucosa and submucosa, with squamous metaplasia of the overlying epithelium. The appearances were ascribed to tracheopathia osteochondroplastica. The patient's stridor gradually improved and within 2 weeks of discharge from hospital, he could walk 4 miles a day. He underwent a further, uneventful general anaesthetic for dental clearance 6 months later.

Discussion

Tracheopathia osteochondroplastica was first properly described by Wilks[2] in 1857 and was initially thought to be rare, as only 245 cases had been described in the world literature until 1974.[3] Tracheopathia osteochondroplastica is a progressive but essentially benign dysplasia of the trachea which is thought to arise as ecchondroses of the tracheal rings.[4,5] Generally, but not invariably, the larynx and pars membranacea are spared.[6] Males and females are affected equally. The disease normally presents after the age of 50 years,[7,8] although it has been described in children.[9] Gradual stenosis of the tracheal lumen produces progressive dyspnoea with an

obstructive spirometric pattern.[8] Patients are usually asymptomatic. Cryptogenic haemoptysis, dry cough and dyspnoea are the recognised presenting symptoms.[4,7]

The benign course of the disease, combined with the lack of awareness of TPO amongst physicians, has, until recently, caused the diagnosis in most cases to be suspected first in the autopsy room,[7,10] the reported incidence being approximately 1 in 400 autopsies.[10] Increasing awareness of TPO over the last 10 years has produced reports of antemortem diagnosis, both by bronchoscopy and by computerised tomography of the trachea; two recent large series put the incidence of TPO between 1 in 125[11] and 1 in 5000 bronchoscopies.[7] Chest radiography has been reported as being rarely helpful[11] but, in our patient and in other reports,[4,10] chest radiography demonstrated stenosing lesions of the trachea, often with a characteristic scalloped outline,[12] which are useful indicators of the presence of TPO.

It is interesting to speculate whether there is an association between the radio-iodine treatment this patient received for his thyroid disease, and the onset of TPO, but there is no information in the literature to support this speculation. Tracheopathia osteochondroplastica was not positively associated with a history of smoking in a review of the literature to 1985. No other aetiological factors have been identified.

Tracheopathia osteochondroplastica has only once been described as a cause of difficulty with tracheal intubation.[8] Knowledge of the condition will prevent unnecessary anxiety for the patient and unnecessary investigation or intervention by medical attendants.[13] The bronchoscopic appearances in advanced cases of TPO are typical,[6,8] but minimal lesions are often missed, even by experienced bronchoscopists.[8] Tracheal biopsy is decisive and eliminates confusion with neoplastic lesions, but extensive calcification can make it difficult to obtain an adequate specimen.[6,14] The primary investigation in a suspected case prior to surgery should be computerised axial tomography of the neck,[4,10,15] as the characteristic appearances of the tracheal lumen allow the diagnosis to be made in all but the mildest of cases.

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APPARATUS

Awareness under anaesthesia due to a defective gas-loaded regulator

G. D. PURI, M. A. GEORGE, H. SINGH AND Y. K. BATRA

Summary

Awareness under anaesthesia occurred in two patients due to a defect in an anaesthesic machine, which caused an inadequate supply of nitrous oxide. A defective fail-safe gas-loaded regulator was found to have caused communication between the pipelines for oxygen and nitrous oxide. This resulted in oxygen flow through the nitrous oxide flowmeter. A simple test to detect this type of defect is suggested.

Key words

Complications; awareness.
Equipment; fail-safe.

Awareness and recall during anaesthesia and surgery, have been reported to occur in as many as 1.2% of surgical patients.[1] Muscle relaxants, inadequate mixture of nitrous oxide and oxygen, use of mechanical ventilators and various defects in anaesthetic machines have been implicated in the causation of awareness during anaesthesia.[2–4] Recently we encountered two patients who reported awareness and intra-operative pain due to a defect in an anaesthetic machine.

Case histories

Case 1

In one patient immediately after skin incision, the pulse rate and systolic blood pressure increased to 140 beats/minute and 150 mmHg, respectively. Signs of light anaesthesia, such as lacrimation and movements of limbs, were also present during this period. Halothane was then added to the anaesthetic mixture. In the recovery room, the patient recalled conversation between the surgeon and the anaesthetist, and also complained that he felt severe pain during the operation.

After this episode, the breathing system of the Boyle apparatus (Mark III, I.O.L.) was checked for any leak or defect in the oxygen flush. With the help of a spirometer, we found no flow in both open and closed breathing systems of the machine when the oxygen and nitrous oxide flowmeter readings were at zero and the emergency oxygen system was in the 'OFF' position.

Case 2

A second patient developed unexpected tachycardia (130 beats/minute) during surgery, but

G.D. Puri, MD, Lecturer, M.A. George, MB BS, Resident, H. Singh, MD, Professor, Y.K. Batra, MD, MNAMS, Assistant Professor, Department of Anaesthesia, Postgraduate Institute of Medical Education & Research, Chandigarh-160012, India.

Correspondence should be addressed to Dr G.D. Puri please.

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this time a higher concentration of halothane was administered. Arterial blood gas analysis at this stage revealed an arterial oxygen tension of 60 kPa. The anaesthetic machine was changed and a repeat arterial oxygen tension measurement with the same anaesthetic mixture (66% nitrous oxide in oxygen), showed a $Pa\text{O}_2$ of 16 kPa. In the recovery room this patient also described hearing sounds and experiencing pain and a burning sensation at the time of surgical incision.

The high arterial oxygen tension in this second patient, suggested that the nitrous oxide concentration delivered to the patient was very low. The nitrous oxide pressure-regulating valves on this anaesthetic machine are of a fail-safe type, so it was thought essential to check these for any defect, since it is at this point that the oxygen and nitrous oxide systems of this machine are in close contact. The nitrous oxide cylinders were removed from the anaesthetic machine, the nitrous oxide flowmeter control was opened and it was seen that the nitrous oxide Rotameter bobbin rose. The nitrous oxide flow could be varied by altering the control valve setting. The gas-loaded regulator for nitrous oxide was examined and found to comprise only a single diaphragm: this diaphragm was cracked (Fig. 1), and thus permitted direct communication between the oxygen and nitrous oxide reduced pressure systems.

Fig. 1. Tear in diaphragm of gas-loaded regulator.

Discussion

The gas-loaded regulator is a type of oxygen failure safety valve of which a standard type is shown diagrammatically in Fig. 2. In this device, oxygen is separated from nitrous oxide in the valve by two interconnected diaphragms and the space between them is vented to the atmosphere, in order to prevent intermixing of the gases in case of any damage to the diaphragm. The gas-loaded regulator in our machine had only a single diaphragm (Fig. 3), so damage to this resulted in the oxygen system coming in contact with the nitrous oxide system. None of the usual anaesthetic machine checks would detect this fault.[5] However, an oxygen analyser in the system would have detected the high $F\text{IO}_2$. We recommend that before connexion of the nitrous oxide cylinders/pipeline to the anaesthetic machine, the nitrous oxide flowmeter should be switched on in the presence of oxygen supply. The presence of flow in the nitrous oxide flowmeter indicates a defect in the oxygen failure safety valve.

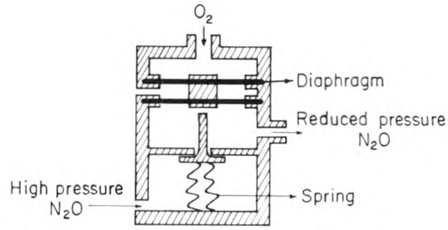

Fig. 2. Line diagram of standard gas-loaded regulator.

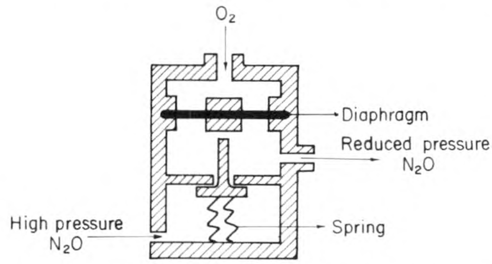

Fig. 3. Line diagram of gas-loaded regulator in the Boyle Mark III anaesthetic machine with a single diaphragm.

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Forum

Intercostal nerve blockade for children

M.P. Shelly*†, FFARCS, Research Registrar, G.R. Park, FFARCS, Consultant in Anaesthesia and Intensive Care, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

Summary

A modified technique of intercostal nerve blockade is described which is suitable for use in children. Ten patients received intercostal nerve blockade on a total of 29 occasions in order to provide analgesia following liver transplantation and to facilitate weaning from artificial ventilation of the lungs. The opioid requirement of patients who received intercostal nerve blockade was considerably lower than that of those who did not; 56% of the children who received intercostal nerve blockade required no additional analgesia. One child, the first to receive intercostal nerve blockade, developed a pneumothorax following the procedure. The technique has proved to be safe in skilled hands. It is an acceptable method of postoperative analgesia in children after liver transplantation and may be a useful technique in the management of other paediatric patients.

Key words

Anaesthetic techniques, regional; intercostal.
Anaesthesia; paediatric.

Interest in nerve and regional blockade for children has been slow to develop. Penile nerve block or caudal analgesia are often used to supplement anaesthesia and provide postoperative analgesia for operations such as circumcision, but other techniques are employed less frequently. Local analgesic blocks in children have a number of problems, particularly for the occasional paediatric anaesthetist.[1] These include the practical difficulties of dealing with small children, their variations from the more familiar adult anatomy, the different equipment or techniques that may be appropriate and the lack of information regarding the pharmacokinetics of local anaesthetics in paediatric patients. The mobility and distress produced by repeated injections in the awake child are a further complication.

Intercostal nerve blockade is used widely in adults, both intra-operatively and for postoperative analgesia;[2] it has also been suggested as suitable for the same indications in children.[3] The risk of pneumothorax is the main disadvantage of intercostal nerve blockade but its reported incidence in adults varies widely[2] and appears to be operator dependent; no incidence has been quoted in children.

Intercostal nerve blockade is performed following liver transplantation in adults, to aid weaning from artificial ventilation of the lungs. Provision of adequate analgesia is difficult in this group of patients since the surgical incision is large: a bilateral subcostal incision with an upward extension to the xiphisternum. Analgesia is required both to allow effective physiotherapy and to reduce the high incidence of respiratory complications following liver transplantation. Opioid analgesics produce sedation and are antitussive. In addition, the elimination of morphine appears to be abnormal in patients following liver transplantation[4] and this may be further exacerbated by impaired renal function.[5]

We have evolved a modification of a standard method for intercostal nerve blockade in order to provide postoperative analgesia for children following liver transplantation. The technique may also benefit other children who require thoracic or abdominal surgery.

* Present position: Senior Registrar, Odstock Hospital, Salisbury, Wilts.
† In receipt of a grant from Napp Laboratories.
Correspondence should be addressed to Dr G.R. Park please.

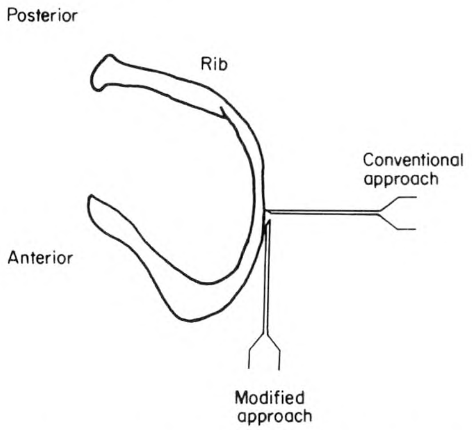

Fig. 1. Position of the needle relative to the rib when intercostal nerve blockade is performed by the conventional and the modified technique.

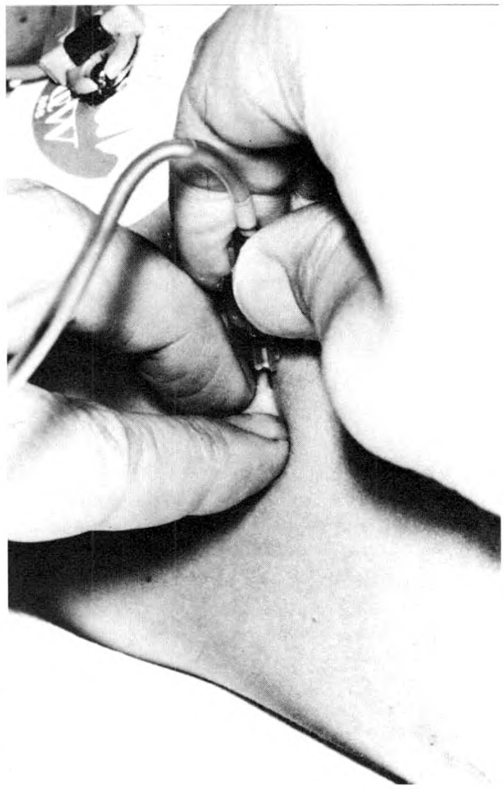

Fig. 2. Position of the hands and needle during intercostal nerve blockade in children using the modified technique.

Methods

Technique of intercostal nerve blockade. The technique of intercostal nerve blockade is a modification of that described for adults in the mid-axillary line.[6] The local analgesic used is bupivacaine without adrenaline; 2 mg/kg are diluted to give a volume of 1 ml for each intercostal space to be blocked. In the smaller child 0.25% bupivacaine is diluted, if necessary, with 0.9% saline to give a final concentration of approximately 0.125%, and in larger children 0.5% bupivacaine is diluted to give an approximate concentration of 0.375%. A 100-cm length of low-deadspace manometer tubing is primed with the solution so that a remote needle technique can be used with a second operator to inject the solution.[7]

The patient is placed in either the lateral or supine position and restrained firmly. The skin is cleaned and the rib palpated in the mid-axillary line. A 25-gauge needle is introduced perpendicularly through the skin onto the rib and gently walked down the rib to its caudad edge. At this point, the needle is angled posteriorly and advanced slightly medially and posteriorly so that it is almost parallel to the rib, until the tip of the needle lies 1–2 mm beneath the edge of the rib. The bevel of the needle faces cephalad (Fig. 1). A loss of resistance is frequently experienced and the needle felt to slide into the subcostal space. The assistant who holds the syringe is asked to aspirate while the needle is held firmly in position, with the back of the right hand supported against the patient and the left hand palpating the rib or steadying the needle (Fig. 2). If no blood or air is withdrawn, 1 ml of solution is injected and the needle removed. It is necessary to block the intercostal nerves bilaterally at T_6–T_{11} inclusive following liver transplantation.

Patients. Twenty children under the age of 10 have undergone liver transplantation at this centre to date. Intercostal nerve blockade was performed in the immediate postoperative period to facilitate weaning from controlled ventilation. Not all of the children received nerve blocks during this period, either because of the absence of an operator familiar with the technique or because of a continuing need for controlled ventilation. Local analgesia was routinely supplemented by bolus opioid administration as necessary to relieve visceral pain.

The records of all 20 patients were reviewed to assess the efficacy of intercostal nerve blockade in this group and the incidence of any complications. To assess analgesic efficacy, opioid requirements on the third postoperative day were converted to morphine equivalents[8] and expressed as mg morphine/kg for that day. Intercostal nerve blocks were performed in the intensive care unit during the first 4 days postoperatively. However, the third postoperative day was chosen to assess analgesic requirements because weaning from artificial ventilation had generally been achieved by this time and pain from the surgical incision was still sufficiently severe to impair respiration as well as to cause distress. At least one erect chest X ray was taken daily in these children, to enable prompt and accurate identification of any pneumothorax.

Results

The 20 children had a total of 21 operations: one patient underwent retransplantation in the early postoperative period. Ten of the children received intercostal nerve blockade on a total of 29 occasions after 11 operations. Ten intercostal nerves were blocked on each occasion. The other ten children did not receive nerve blocks; analgesia was provided in these cases by intravenous opioids.

Analgesic requirements on the third postoperative day were not determined for seven cases. Two cases received intercostal nerve blockade as part of their postoperative analgesic regimen but this was omitted on the third postoperative day because no skilled operator was available. The other five patients did not receive intercostal nerve blockade; two had died by the third postoperative day and information for the other three was incomplete and analgesic requirements could not be assessed for that day. The details of the 14 patients whose analgesic requirements were reviewed, are shown in Table 1. Nine of the patients received intercostal nerve blockade and their tracheas were extubated on or before the third postoperative day. Of the five patients who did not receive intercostal nerve blockade, two were extubated on the third postoperative day; the other three received controlled ventilation.

Table 1. Details of patients.

	Intercostal block (n = 9)	No block (n = 5)
Mean age, years (range)	3.7 (1.1–7.0)	2.8 (2.0–3.5)
Sex; M:F	4:5	2:3
Mean weight, kg (range)	14.2 (10–22)	12.8 (8–22)
Diagnosis		
Biliary atresia	6	3
Neonatal hepatitis	1	1
Alpha-1-antitrypsin deficiency	1	—
Drug-induced	1	—
Angiocarcinoma	—	1

The nine patients who received intercostal nerve blockade required a mean dose of 0.16 mg/kg morphine (SD 0.27) on the third postoperative day; the corresponding dose in those who did not receive the nerve block was 1.52 mg/kg (SD 0.93). All patients who did not receive a nerve block, required opioid.

The three patients who still required controlled ventilation on the third postoperative day had more severe illness and were sedated with midazolam in addition to morphine. They received a mean of 1.04 mg/kg morphine on that day; the two patients whose tracheas were extubated on the third postoperative day, however, received a mean of 2.25 mg/kg morphine on that day. Most of the children received intercostal nerve blockade on two or three occasions during and after weaning from artificial ventilation. The duration of analgesia on each occasion was approximately 12 hours.

The complication rate of the technique was low. Two of the 20 children developed a unilateral pneumothorax, but one child had not received intercostal nerve blockade, while the other had received intercostal nerve blockade 3 days previously and was the first patient on whom the technique was performed. The children frequently slept after administration of the blocks; none had evidence of systemic local anaesthetic toxicity. Two patients developed sputum retention after early discharge from the intensive care unit. Both received intercostal nerve blockade initially but were subsequently given relatively high doses of morphine for analgesia and sedation on the ward.

Discussion

Children who undergo liver transplantation are a small but uniform group. Few other abdominal procedures are performed in children, that require the same degree of effective analgesia to relieve severe postoperative pain over a prolonged period. Intercostal nerve blockade is an established and effective technique for intraoperative and postoperative analgesia in adults.[2] Use of the technique has been shown to reduce postoperative opioid requirements and respiratory impairment.[3] The main disadvantage is the incidence of pneumothorax and, in children, the smaller anatomical distances involved may increase this risk. A midaxillary approach is used in the technique described above to reduce the likelihood of pneumothorax.[9] The risk of pleural puncture is further decreased because the needle enters the intercostal space at an acute angle, almost parallel to the rib. Thoracic epidural analgesia is not employed in these patients because of the bleeding disorders frequently encountered in patients with liver disease, and the risk of hypotension due to sympathetic nerve blockade.

Intercostal nerve blockade has a number of advantages over opioid analgesia following liver transplantation. A large surgical incision is present and adequate analgesia without profound sedation may be difficult to achieve with opioids. Postoperative respiratory complications are common in patients following liver transplantation, and good pain relief with a cooperative patient and without respiratory depression is essential for effective physiotherapy. The importance of these points is illustrated by the two children who developed sputum retention due to sedation following opioid analgesia. A postoperative ileus invariably develops after liver transplantation and recovery of effective gastrointestinal motility is hastened if the opioid dose can be reduced. The antidiuretic effect of morphine may further impair already compromised renal function in these patients. Adequate renal function is important in the elimination of morphine[2] and, if impaired, may exacerbate the abnormal elimination pattern already present in these patients.[4] Opioid-induced nausea and peripheral vasodilatation may also

cause problems which can be avoided by intercostal nerve blockade. This study reports only a small number of patients but the use of intercostal nerve blockade immediately prior to weaning from artificial ventilation, and repeated as necessary afterwards, reduced opioid requirements significantly during this period.

The complications of intercostal nerve blockade include pneumothorax, haematoma formation and local anaesthetic toxicity from inadvertent intravascular injection. One child who received intercostal nerve blockade suffered a small unilateral pneumothorax but that occurred 3 days after his last intercostal blockade. Since he was the first patient to receive a block, this may reflect lack of experience of the technique; no subsequent patient developed this complication. Pneumothorax is a complication of artificial ventilation itself, particularly in children, and one other child who did not receive an intercostal block, also suffered a unilateral pneumothorax. The pneumothorax in this patient was associated with barotrauma during controlled ventilation of noncompliant lungs following the development of respiratory distress syndrome after inadvertent administration of cyclosporin into a central vein.[10]

All patients had slightly impaired clotting indices at the time of the blocks but neither bleeding nor haematoma formation proved a problem. Systemic local anaesthetic toxicity was not observed, although a maximum bupivacaine dose of 4 mg/kg has been recommended,[11] but a dose of 2 mg/kg was administered to these patients because of their impaired liver function. Sleep following intercostal nerve blockade was a consistent feature. This may be due to several factors: sedation is a side effect of local anaesthetic agents and may be particularly apparent when relatively large doses are used or when rapid uptake occurs; satisfactory analgesia may cause a tired child to sleep; and, finally, the performance of the blocks or subsequent physiotherapy may themselves tire the child. Although sleepy, the children were always rousable and cooperative. No other complications of the procedure have been noted and the children appeared to forget quickly the temporary discomfort of the repeated injections.

The modified technique of intercostal nerve blockade described, has been found to provide effective postoperative analgesia with a reduction in opioid requirements.

Acknowledgments

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Assessment of alfentanil by intravenous infusion as long-term sedation in intensive care

A.T. Cohen, MB,ChB, DRCOG, FFARCS, Consultant, D.R. Kelly*, MB,ChB, FFARCS, Senior Registrar, The Intensive Care Unit, St. James's University Hospital, Beckett Street, Leeds LS9 2TF.

Summary

The use of an alfentanil infusion for sedation of critically ill patients in intensive care was investigated in 16 patients who were entered consecutively into the study. The mean duration of stay was 8 days. Supplements of Diazemuls and muscle relaxants were administered if required. The success of the technique was judged by nursing and medical staff and, in particular, the wakefulness of patients was noted. No patient could recall events that occurred during their infusion. An outline protocol is described.

Key words

Analgesics; narcotic; alfentanil.
Intensive care.

There has been a gap in the therapeutic armamentarium of the intensive care physician since the withdrawal of Althesin and the discovery of the deleterious effects of etomidate on cortisol production.[1] Patients who undergo long-term ventilation of their lungs require some form of sedation, especially during the early part of their treatment; a hypnotic or analgesic, with or without muscle relaxant, is frequently used. An ideal sedative should produce a comfortable, pain-free patient who will comply with imposed ventilation but is not necessarily asleep.

Many modern intensive care ventilators incorporate a synchronised intermittent mandatory ventilation (SIMV) mode which allows the patient to breathe spontaneously between mandatory breaths. When SIMV is used routinely, the incidence of 'fighting the ventilator' is minimised and the necessity to use muscle relaxant drugs is therefore reduced. Long periods of unbroken sleep induced with infusion of hypnotic drugs (such as the benzodiazepines) may be undesirable, so we decided to concentrate on the use of nonhypnotic drugs such as opioid analgesics. A drug suitable for long-term sedation in intensive care should be noncumulative, and not result in significant cardiovascular or other side effects.

Alfentanil, a synthetic fentanyl analogue, has been shown to be a safe, short-acting narcotic, with a rapid onset and offset of action, easily reversible by naloxone, with remarkable cardiovascular stability and compatible with administration by intravenous infusion.[2–5] The short elimination half-life and low volume of distribution indicate that accumulation will be less significant than with more conventional narcotics and that it may be a suitable drug for use by infusion in intensive care.[6] The aims of this study were to assess the clinical acceptability to staff and patients, of alfentanil as an agent for long-term infusion in a general intensive care unit, and to establish a suitable administration protocol.

Methods

The study was approved by the local ethical committee and consent was sought from the patient or next of kin. Any patient in whom a narcotic infusion would normally have been used for a period of 24 hours or more, was entered sequentially. No patient with significant hepatic dysfunction or head injury was studied and, for practical reasons, only one patient was studied at a time.

The infusion protocol guidelines were formulated as follows. A bolus of 25 μg/kg was given over 60 seconds prior to commencement of the alfentanil infusion. The infusion was then administered via a volumetric infusion pump (IMED 960) at an initial rate of 0.67 μg/kg/minute for 20 minutes followed by a rate between 0.1 and 2.0 μg/kg/minute. Boluses of alfentanil (3 μg/kg) were administered if the infusion was determined inadequate, and electively with each stimulating procedure such as tracheal suction and physiotherapy. Inadequacy was defined as noncompliance with ventilation or excessive increases in pulse and blood pres-

* Present position: Consultant, Victoria Hospital, Whinney Heys Road, Blackpool FY3 8NR.

sure. The infusion rate was increased by 0.1 μg/kg/minute if more than two nonelective doses were required in any 30-minute period. Similarly, the rate was reduced if no supplements were required in a 30-minute period until a steady state was achieved. Most patients required additional sedation which was provided by Diazemuls 0.075–0.125 mg/kg. Diazemuls was administered to produce sleep during unpleasant stimuli, such as changing a tracheal tube, electively at night when clinically indicated, especially in long-stay patients, or if excessive narcotic supplements were required, as judged clinically for example by exceeding the maximum recommended dose of alfentanil. Muscle relaxants were used in patients if the ability to ventilate the lungs was compromised by extreme compliance problems, or in the presence of severe hypoxia.

Noncompliance with ventilation was scored hourly as in Table 1 by the nurse responsible for the patient. In addition, systolic and diastolic arterial pressure, central and peripheral temperature and mean infusion rate were recorded hourly. Further records were made of peak pulse and blood pressure response to stimulating procedures such as physiotherapy, of narcotic, sedative and relaxant supplementation, of the condition of the vein, of daily blood chemistry and (three times weekly) of liver function. The alfentanil infusion was discontinued when judged clinically to be no longer required. Any delay in the onset of spontaneous ventilation was recorded.

After discharge, nursing and medical staff were asked to score the quality of the sedation technique as: 0, perfect; 1, good but not perfect; 2, acceptable; 3, poor; 4, unacceptable. The patients were visited by one of the investigators on the ward and they were questioned to see what they remembered of their stay in the intensive care unit. A patient comfort score was recorded: 0, no recall; 1, completely comfortable; 2, uncomfortable at times; 3, uncomfortable most of the time; 4, suffered unbearable discomfort.

Results

Sixteen patients were studied; their ages ranged from 17 to 80 years, and there were equal numbers of males and females. Table 2 provides demographic information and details of the diagnoses. The mean duration of stay was 8 days and 70% of the patients survived.

Infusion rate. Each infusion was tailored to the patient's requirements. The principles of the infusion protocol were followed, but some of the doses were found to be inadequate. We also found that many patients admitted to the intensive care unit were already sedated and did not require a bolus of alfentanil and initial higher infusion rate. In order to transform the large quantities of infusion data into manageable numbers, the infusion rate in μg/kg/minute (IR_d) was calculated for each patient day during the period of the infusion, by dividing the total dose of alfentanil administered per day by time and weight. Infusion rates were quite variable

Table 1. Scoring system used to assess degree of sedation.

Score	Degree of sedation
0	Asleep, no response to tracheal suction
1	Rousable, coughs with tracheal suction
2	Awake, spontaneously coughs or triggers ventilator
3	Actively breathes against ventilator
4	Unmanageable

both between and within patients, from a maximum of 2.5 μg/kg/minute to a minimum of 0.08 μg/kg/minute. There was no evidence of correlation between infusion rate and duration of infusion, which would have confirmed tolerance; however, it is probable that this could have been masked by diminishing requirement for sedation as patients improved and became used to the ventilator. To facilitate between-patient comparison, the total amount of alfentanil administered to each patient during the study was calculated and expressed as μg/kg/minute (IR_t). The IR_t varied from 0.11 to 2.18 μg/kg/minute, with a significantly lower requirement in the older patients (over 50 years) than the younger ($p < 0.05$, Student's *t*-test): the respective mean (SEM) values were 0.4 (0.03) and 1.0 (0.08) μg/kg/minute.

Hourly sedation score. The commonest score taken from the chart was recorded daily and in no case was this as high as 4. Most patients were well sedated and easy to manage; no patient was withdrawn from the study because of failure of the technique to provide satisfactory conditions. The numbers of scores for each patient in each category (expressed as percentages) can be seen in Table 3; over 75% of scores were less than 3.

Cardiovascular side effects. There was no evidence of significant cardiovascular side effects associated with the use of the drug even when boluses were administered. The problem of bradycardia seen occasionally by the authors when the drug was used by infusion in the operating theatre, was completely absent even with the high infusion rates used in some patients.

Respiratory depression. The majority of patients in this study were ventilated in the SIMW mode and contributed significantly to their minute volume in spite of being on an alfentanil infusion; however, the initial apnoea associated with the drug, was often useful in settling the patient on intermittent positive pressure ventilation. All patients were awake and ready to breathe before the alfentanil was switched off. In those cases that required analgesia, the infusion was continued into the post-weaning period. Wakefulness in the presence of analgesia helped patients cooperate with physiotherapy. Naloxone was not used in any patient.

Supplements. The mean rate of supplementation was 2.5 doses of Diazemuls per patient day. Many patients were aware of their surroundings and required occasional supplementation to allow sleep. Others required supplementation to aid maintenance of cardiovascular stability.

Table 2. Demographic and infusion data. Total doses of Diazemuls and relaxant are shown.

Patient number	Diagnosis	Infusion time, days	Weight, kg	Age, years	Alfentanil infusion IR_r, µg/kg/minute (IR_d range)	Diazemuls, mg	Pancuronium (atracurium), mg
1	Pneumonia/bone marrow transplant	5	44	20	0.58 (0.76–0.49)	45	78
2	Respiratory failure/COAD	2	65	62	0.34 (0.38–0.26)	80	
3	Fat embolus/fractured femur	9	50	17	2.18 (2.50–1.42)	285	148
4	'Failure to reverse'/COAD	14	65	66	0.17 (0.26–0.13)	95	
5	'Failure to reverse'/COAD	15	75	67	0.35 (0.73–0.17)	135	20
6	Goodpasture's syndrome	49	75	33	0.46 (1.14–0.08)	555	118 (790)
7	Flail chest	3	80	56	0.31 (0.63–0.22)	25	
8	Aortic surgery/respiratory failure	1	76	68	0.11 (0.11–0.11)	5	
9	Hysterectomy/respiratory failure/COAD	15	55	73	0.33 (0.61–0.17)	35	
10	Oesophageal varices/respiratory failure	3	69	40	1.22 (1.45–0.97)	5	
11	Respiratory failure/COAD	2	59	67	0.51 (0.56–0.35)	40	(650)
12	Eaton-Lambert syndrome	4	61	80	0.41 (0.55–0.19)	10	
13	Pulmonary aspiration	2	70	74	1.15 (1.19–1.01)	50	52 (120)
14	Systemic lupus erythematosus	2	63	19	0.54 (0.54–0.54)	20	
15	Status asthmaticus	1	59	19	0.92 (0.99–0.88)	55	40
16	Legionnaires' disease	4	66	47	0.80 (1.01–0.25)	50	

COAD, chronic obstructive airways disease.

Table 3. Frequency of sedation score in each patient expressed as a percentage.

Patient	Sedation score				
number	0	1	2	3	4
1		38	62		
2			100		
3	30	35	34	1	
4	17	61	21	1	
5		34	56	10	
6	3	46	47	4	
7			60	40	
8		24	56	20	
9	6	12	50	33	
10		7	80	13	
11	23	25	46	6	
12	4	12	67	17	
13	28	69	3		
14		84	16		
15		100			
16		73	27		

Relaxants. Seven of the 16 patients were paralysed at some stage of their therapy after intubation. The doses can be seen in Table 2.

Hepatic function. No effect on liver function was detected despite the large doses of alfentanil used in some patients. In one case this amounted to 4913 ml over a period of 49 days.

Disadvantages. No complications were seen except occasional wakefulness, which was disturbing to staff unfamiliar with the technique.

Acceptance. No patient could remember their stay in intensive care. Apart from comments about the wakefulness, medical and nursing staff were happy with the technique.

Discussion

Opioid drugs have been used for some years in intensive care to sedate patients but, despite extensive experience, there is very little written about their usefulness and effects. Our experience with current sedative techniques is that problems can arise from slow onset of action, delayed gastric emptying and accumulation that results in drowsiness and delayed weaning. We felt that alfentanil could offer an alternative; its rapid onset of analgesia and respiratory depression facilitate initial settling on ventilation, while it has a potential for minimal accumulation.

No studies are available about the long-term use of alfentanil as a sedative in intensive care. However, it has been used successfully during surgery with a recommended infusion rate of 0.5–1.0 µg/kg/minute, and in the postoperative period at a rate of 0.33 µg/kg/minute, without significant ventilatory depression.[7]

Requirements for analgesia and sedation in intensive care patients vary considerably, so a variable infusion rate protocol was devised based on the current dosage recommendations from earlier studies of surgical patients. Infusion rates varied in each patient and it was difficult to establish what effects were caused by the individual gradually becoming more used to ventilation while possible tolerance to alfentanil developed concurrently. There appeared to be two groups separated by age: those over 50 years with a mean infusion rate of 0.4 µg/kg/minute, and those less than 50 years with a mean infusion rate of 1 µg/kg/minute. Between-patient variability has been discussed by many investigators and it is clear that more work needs to be done to study the effects of age, obesity, hepatic blood flow, hepatic function and protein binding before anything but trial-and-error techniques can be used to ascertain initial and maintenance infusion rates in the critically ill. Intensive care patients are not subjected to such

Table 4. Details of alfentanil infusion regimen.

Treatment	Comments	Infusion rate, μg/kg/minute
Sedative infusion	initial rate	0.5
	increment/decrement	0.25
	maximum rate	2.0
	minimum rate	0
Spontaneous ventilation	depends on duration of infusion (tolerance)	0.2
Bolus	not necessary at beginning of infusion administer prior to painful procedures	10–20 μg/kg
Supplements	hypnotics	e.g. 0.1 mg/kg Diazemuls
	relaxants	e.g. 0.5 mg/kg atracurium

Adolescents and young adults may require higher than average doses.

It can be hard to detect overdosage of alfentanil; consequently, it is possible to use more than is required or to maintain an unsuitably high infusion rate. Alfentanil is administered to keep the patient comfortable, not asleep, and it is important that efficacy of the infusion is assessed regularly and appropriate increases or decreases made to the rate, with special effort to reduce it to that consistent with spontaneous ventilation unless there are contraindications.

Administration of naloxone is almost always inappropriate in these patients except for assessment purposes. Alfentanil may have a prolonged effect after a long infusion.

severe forms of peroperative stress as surgical patients, and for long periods their requirements for sedation and analgesia may be far less than required for stimulating procedures such as physiotherapy. Table 4 contains a summary of the infusion protocol developed from this work and currently used in our intensive care unit.

The quality of sedation was good. The nursing staff rapidly became familiar with the drug and the scoring system, and altered infusion rates accordingly. Diazemuls supplementation was part of the protocol because we felt the necessity to include an hypnotic component. Early in the study nursing staff requested this supplementation comparatively frequently, as they were unused to seeing awake ventilated patients. However, later they realised that the patients were in fact comfortable and able to aid with physiotherapy and communicate with staff and relatives. Delayed response to weaning due to accumulation of alfentanil was not seen, and this was thought to be due probably to tolerance to the respiratory effect of the drug when administered by infusion over a period of time.

We do not routinely paralyse patients who require long-term ventilation of the lungs; however, seven patients were paralysed, which reflects the nature of the group of patients studied. The only problems raised by the use of this technique were due to unfamiliarity of the less experienced staff with the wakefulness seen, and to the cost of alfentanil when used in the quantities sometimes necessary. Overall, we were impressed with the very rapid onset of action of the drug and its apparent lack of accumulation. Overdosage is not apparent until attempts are made to wean the patient, because of the lack of side effects. This makes a policy of continual assessment of the efficacy of the infusion important, with appropriate increases or decreases in infusion rate. The ability to administer a rapidly acting bolus of the drug is very useful when painful procedures are anticipated.

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Correspondence

All correspondence should be addressed to Dr J. N. Lunn, Editor of *Anaesthesia*, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, United Kingdom.

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A way forward for intensive care

In his recent editorial (*Anaesthesia* 1986; **41:** 1181–3), Dr J.C. Stoddart reviews the growth of intensive care and highlights some of the problems of identity, clinical responsibility and training which have bedevilled it the world over. Few would dispute that it has been contentious, destined to provide a service to patients from any clinical specialty and, in so doing, it derives expertise from anaesthesia (mechanical ventilation), cardiology and cardiac surgery (pacing, support for the failing circulation), nephrology (dialysis) and neurosurgery (intracranial pressure monitoring), to name but a few of the technical skills alone.

A high proportion of those who currently contribute to intensive care in the UK, favour the concept of a multidisciplinary service and welcome the recommendations of the Interfaculty Liaison Committee on the content of a suitable training programme and how it might be achieved by applicants from diverse backgrounds. While it is recognised that interdisciplinary exchange may prove impractical, an anaesthetic Senior Registrar is no more able to undertake the duties of his physicianly or surgical colleague than *vice versa*, recognition of the difficulty is no reason for not trying to achieve the objective. The creation of additional training posts might be preferable but is probably unrealistic, on financial grounds if none other. Secondment of those who seek a career in intensive care could be more practical. An analogy can be drawn with current schemes which allow trainees to obtain experience of research, or work abroad, without necessarily losing allegiance to their primary discipline. In practice this might go a long way to prevent the potential difficulties envisaged by Dr Stoddart, who foresees the creation of a pool of well-trained, but unfulfilled, intensive care specialists too far divorced from their parent discipline to practice it either at the outset of their Consultant career or later, as well as an obligatory allocation of intensive care sessions to Consultant posts in all specialties.

In the course of resolving this possible source of yet more conflict, it is essential that we recognise not only the necessity to provide a first class service to patients but also the complementary nature of today's varied medical skills and the benefits which result when staff of differing backgrounds work together harmoniously. A system of intensive care devoid of the input of anaesthetists is inconceivable. To claim it as the sole prerogative of anaesthetists would be a retrograde step, and belittle us and our specialty.

Brompton Hospital,
London SW3 6HP
M. BRANTHWAITE

The aim of the training programme is surely to provide for better patient care rather than to endorse the concept that 'intensive therapy and anaesthesia go naturally together'. The patient who is critically ill may require expertise in a variety of areas and, while the 'intensive anaesthetist' who works in a teaching centre has immediate access to experts in renal medicine, thoracic medicine, cardiology, neurology, radiology, microbiology and chemical pathology, these facilities may not be available to the clinician who works in a District General Hospital. It therefore seems logical and important that the expertise of anaesthetists and physicians should be pooled together in a coordinated training programme where each discipline can be enriched by interdigitation with the other. In the historical evolution of intensive therapy units the anaesthetist was the natural guardian of ventilatory support but, with the advancement of knowledge, skills and techniques in the care of the critically ill, none need to be sacred to any one discipline.

In the current climate many young doctors are no longer attracted to a career in hospital medicine, especially if there is no structured plan. The concept of a coordinated programme which rotates through various disciplines appropriate to the management of the critically ill, must surely have appeal for anyone concerned with giving overall best care to our future patients.

In welcoming this training programme one is not denying the fact that pitfalls may arise and, indeed, they should be anticipated, especially in the light of knowledge gained from experience in other countries. However, the long-term objective is better patient care. The aim to have more broadly based clinicians with specific orientation to the management of the critically ill, must surely override any potential interdisciplinary rivalries.

Many of the current clinicians involved with the evolution of intensive therapy units have gained their experience on an *ad hoc* basis. The time has surely come for us to produce the second-generation intensive care clinician who has undergone a structured training programme with a multidisciplinary input.

The Royal Free Hospital, London NW3 D.R.G. BROWNE

Dr Stoddart highlights a number of important problems which remain to be resolved before the recommendations of the Joint Liaison Committee for training in intensive care can be finally implemented. It is clearly essential that such practical difficulties are identified but they must not be allowed to stifle this vital initiative at its inception; they can surely be overcome given goodwill and determination from all those involved.

The suggestions of the Joint Liaison Committee have been produced in order to rectify the absence of adequate formal training for those who wish to specialise in intensive care. The knowledge and experience which must now be assimilated by those who wish to pursue a career in this specialty, is so extensive (witness the size of recently published reference books) that it cannot possibly be acquired on an *ad hoc* basis as part of general or higher professional training in anaesthesia or general medicine, nor can it be satisfactorily incorporated within existing postgraduate examinations such as the FFARCS and MRCP. Certainly, in the larger institutions, Consultants who devote all, or at least the major part of their time to intensive care should have been trained to the same level of expertise in their specialty as, for example, cardiologists are in theirs. Viewed from this perspective a two-year apprenticeship does not seem unreasonable. Moreover, it will also prove necessary, sooner or later, to consider ways in which to improve the training of Consultants with an interest in intensive care, who work in smaller units. These measures are necessary not only to improve standards of patient care but also to foster research, in which we unfortunately lag far behind North America and the rest of Europe.

Most would agree with Dr Stoddart that anaesthesia is the base specialty most suited to the practice of intensive care medicine and it is likely, therefore, that anaesthetists will continue to dominate the specialty. Nevertheless, intensive care is already multidisciplinary and, currently, many of the foremost authorities in the United Kingdom were trained primarily as physicians or surgeons; to claim that intensive care is exclusively the province of the anaesthetist is, therefore, not longer tenable. Moreover, if this proposal were implemented it would prevent many talented young physicians from making their contribution to the discipline. By cooperation with the present multidisciplinary approach anaesthetists will guarantee their dominant position in the future development of the specialty, whereas an isolationist policy will almost certainly lead to fragmentation and continuing conflict.

This is not, as Dr Stoddart suggests, a relatively small problem but rather a major issue which must be tackled in order to provide enthusiastic young doctors with the best opportunity to participate in the development of an expanding discipline.

St Bartholomew's Hospital, London EC1 C.J. HINDS

Dr J.C. Stoddart's editorial on the Inter-Faculty/Collegiate Liaison Group's recommendations on training in intensive therapy is a curious mixture of pertinent questions and surprising misunderstandings. Inevitably, the problems of finding medical jobs for anaesthetists (and anaesthetic jobs for physicians), of manpower and of the length of time a Consultant may expect to be at the sharp end of intensive therapy, have not yet been solved. It is precisely for this reason that the Liaison Group is moving forward only gradually. As we understand it, it is certainly not the intention to produce large numbers of intensivists no longer suitable to practise their parent specialty, nor indeed to increase the number of trainees.

Much more important, however, are the misunderstandings. Dr Stoddart believes that the problem which the proposals intend to resolve, is the recognition that intensive therapy and anaesthesia go naturally together. It is not. The objective of the proposals is to improve the standard of training of those Senior Registrars who want a Consultant post with intensive care as its major component. They seek to do this within the framework of what is actually happening in intensive therapy in this country, namely, that some physicians and a few surgeons, as well as anaesthetists, do look after intensive therapy units. There are trainees in these disciplines, as well as in anaesthesia, who aspire to Consultant posts with a major intensive care component. Our colleagues in America and Australia have failed to produce a common training programme. Are we to follow? On the contrary, the agreement so far secured between the Royal College of Surgeons, the Faculty of Anaesthetists and the Royal College of Physicians is remarkable, if not unique.

It is to the enormous credit of anaesthetists, among whom Dr Stoddart has been foremost, that they have provided the greater part of the manpower and expertise for intensive care in the United Kingdom. They will continue to do so. However, it is increasingly recognised that Senior Registrars need training in several areas of intensive therapy which they do not receive during general professional training, in particular in the recognition and management of patterns of organ failure. We hope that our pilot scheme in the South West Region will demonstrate that this can be

achieved. We believe that anaesthetists have nothing to fear from these proposals, aimed as they are at improving the care of critically ill patients.

Bristol Royal Infirmary, S.M. WILLATTS
Bristol BS2 8HW
Royal Devon and Exeter Hospital, J.F. SEARLE
Exeter EX2 5DW

It is rather depressing to find at the end of an otherwise thoughtful leading article (*Anaesthesia* 1986; **41:** 1181–3), the statement that 'anaesthesia and intensive care go naturally together'. Training in anaesthesia, whilst useful, is not essential for intensive care. The practical skills required can be learned reliably in the ITU itself, and the therapeutic aspects are as much medicine as anaesthesia.

It is an historical accident, rather than logic, which has placed anaesthetists in charge of the majority of ITUs, frequently, as Dr Stoddart points out, without proper sessional recognition. This haphazard arrangement has resulted in many excellent ITUs but the time has come to recognise that individuals trained in other specialties, particularly medicine, have an important part to play. Of those physicians who are currently in charge of intensive care units many are leaders in the field. The current system, however, discriminates against anyone who, whilst interested in intensive care, feels unable for reasons of temperament or aptitude, to train as an anaesthetist. Many anaesthetists are not interested in intensive care. The converse is also true.

The pilot schemes for training in intensive care are thus a welcome step. They will be, for the moment, restricted to those who have completed Higher Professional Training in their major subject. These individuals will therefore be credible as Consultants in their major specialty, and could return to it after a few years. Let us hope that some imagination will now be displayed in providing Consultant posts with sessions in ITU for nonanaesthetists. Unless such posts are created many current physicians in training will find their intensive care skills wasted.

Nuffield Department of Anaesthetics, C.R. BLAKELEY
Radcliffe Infirmary,
Oxford OX2 6HE

A reply

Thank you for the opportunity to reply to some of the letters which were provoked by my recent editorial. The problem which is being addressed is that of management and clinical care in an intensive therapy unit.

The letters from Drs Browne, Hinds, Blakeley, Willatts and Searle require from me only a general statement to the effect that I agree entirely that whoever runs an intensive therapy unit (ITU) should be properly trained so that patients can receive the necessary treatment. Dr Branthwaite's letter requires a more detailed reply.

What is the evidence for the statement that a high proportion of those who currently contribute to intensive therapy, favour a multidisciplinary approach to management? The Intensive Care Society has this as its aim but, as a founder member and ex-Chairman of the Society, I am not aware that one needs to make a public declaration of this opinion to become a member. Nevertheless, I would be the first to agree that no single clinician (armed with even the biggest book, *pace* Dr Hinds) can handle all of the problems presented by the patient in the ITU, and the final paragraph of my editorial clearly stresses this.

Dr Branthwaite implies, although I am sure she does not intend to, that the anaesthetist's contribution to the technology of intensive therapy is via controlled ventilation of the lungs. Even in the absence of the kind of additional training which I suggested was necessary, the anaesthetist has made a much greater contribution than this.

The Joint Liaison Committee intends that trainees of Senior Registrar status should have a multidisciplinary training. It is not suggested that either the physician or anaesthetist trainee requires surgical training. Nevertheless, such trainees will be Senior Registrars by salary scale only, since none can expect to assume the equivalent responsibilities in a new specialty. However, I believe that a surgical or anaesthetic registrar would be more immediately useful in medicine than would either of the others in anaesthesia.

The analogy which is drawn between specialist training in intensive therapy and either a research post or a period of work abroad is, in my opinion, a false one. Most such programmes are entered with a specific end in view which is directly related to the primary discipline and for which credit is given at the appropriate time, that is, at the Consultant appointment interview. Unless the post which is being filled includes recognised sessions in intensive therapy, I doubt whether a putative physician or surgeon would be given much credit for 3 years outside his chosen specialty, in anaesthesia and intensive therapy, although it would be of unquestionable value to him. This was the point of the editorial. Anyone can design a practical training scheme for intensive therapy—I have done so myself—but, unless such posts are to be established outside anaesthesia, I consider that the trainees may be misled as to their ultimate prospects.

Finally, although I did not state that intensive therapy should be the prerogative of anaesthetists, but only that they appeared to me to be the most fitted for it, I fail to see how, by making such a statement, the specialty of anaesthesia could be belittled.

The Royal Victoria Infirmary, J.C. STODDART
Newcastle-upon-Tyne NE1 4LP

The whole question of training for a career in intensive therapy has been thrown into sharp focus by the recent leading article in your journal and Dr Stoddart is to be congratulated on re-opening the debate on this important issue. That there is a need to improve standards of training is not in dispute. There must always be room for improvement. The proposed training scheme is not, however, the correct way forward.

It is proposed initially to create two posts at Senior Registrar level for individuals who have been accredited in their parent specialty. These trainees would expect to train for an additional 2 years before taking up posts with a large intensive therapy sessional commitment. It is difficult to see what such a scheme would achieve except to produce a small elite. The creation of as many as a dozen such training posts would, I contend, have little impact on the overall level of patient care, even if it is assumed that suitable Consultant posts could be found.

The need is much more mundane, and that is for the intensive therapy content of training posts at Senior Registrar level to be increased generally. The ability to manage critically ill patients is essential even for those who do not seek a career in this field. A very large number of anaesthetists are, and will continue to be, directly involved in managing critically ill patients and this needs to be recognised. Our efforts should be directed to improving their training and I am concerned that the training programmes suggested will serve merely to reduce their opportunities.

The Faculty of Anaesthetists has tried to include intensive therapy in the curriculum of every trainee and many posts offer excellent training in this field, whilst a few offer only limited experience. This is probably as it should be since trainees do not all have the same aspirations, but posts that offer experience in intensive therapy should be recognised and any expansion of the training programme should centre on them, with consequent benefit to large numbers of trainees and their future patients.

It is to be hoped that representatives of the Faculty of Anaesthetists will continue to meet with the Liaison Group but they should, in my view, be stating clearly that the scheme presently being discussed is not acceptable.

Morriston Hospital, E. MAJOR
Swansea SA6 6NL

Pre-operative visits

The letter from Professor Hunter (*Anaesthesia* 1986; **41:** 1161–2) was interesting since I had similar feelings on reading the article[1] to which he referred. However, it is a pity that Professor Hunter apparently condones and accepts a low level of pre-operative visits by anaesthetists.

There are several reasons to consider a pre-operative visit by an anaesthetist to be an essential part of anaesthetic practice. The most obvious is to make an assessment of the patient's condition, particularly with regard to those points which may be of significance during the conduct of the proposed anaesthetic. This aspect of the visit must have considerable medicolegal significance, even with regard to minor complications. How can one say that damage to unstable dentition was inevitable if the patient had not been seen, assessed and the possible complications explained by the anaesthetist? There are many other points whose significance may be lost to the nonanaesthetic assessor, and avoidable injury which could have been prevented if the condition had been recognised at a pre-operative visit, would be difficult to explain to the patient or to defend in the event of litigation.

A pre-operative visit by the anaesthetist, coupled with an explanation of the procedure, frequently provides sufficient reassurance to make pharmacological premedication unnecessary.

The image of the individual anaesthetist and of anaesthesia in general, both in the eyes of our colleagues and our patients, depends to a large extent on pre- and postoperative visits. The patient whose only acquaintance with anaesthesia is to meet an anonymous figure in the anaesthetic room, may have just cause to be surprised that anaesthetists have to be medically qualified and are not selected and trained by the surgeon.

The nursing staff on the ward will never understand the role of the anaesthetist in the management of the patient and, indeed, if the anaesthetist does not visit the ward he may never realise that the perfect theatre anaesthetic may be followed by minor sequelae that include avoidable pain and nausea.

Finally, it is very difficult to maintain an equal position in discussion about a patient with a surgeon unless one has already seen the patient: quite rightly, the views of someone who has neither visited nor assessed the patient tend to be disregarded. Personally, I feel uneasy about the anaesthetic on the rare occasions on which I first meet a patient in the anaesthetic room.

There is no question that the practice of pre-operative visiting has become more tedious over the years; 20 years ago patients for cardiac surgery were admitted 3 or 4 days pre-operatively, now they are liable to arrive late on Sunday for operation on Monday. Day case surgery may involve visits to 10–15 patients before the morning list starts. Despite all the problems, my opinion is that visiting patients pre- and postoperatively

is an essential part of the professional role of the anaesthetist and that every time a patient is anaesthetised by someone he has never met, our profession is belittled.

Rather than seeing letters which deplore the low incidence of pre-operative visits, I would prefer to see the leaders of our profession using the correspondence columns of *Anaesthesia* to insist that no new appointment be made, at any grade, where there is inadequate opportunity to visit patients before and after operation and that recognition for training should be withdrawn from any hospital where anaesthetists do not routinely visit their patients.

Papworth and Hinchingbrooke Hospitals, Cambridgeshire D.W. Bethune

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Postmortem removal of tracheal tube

My colleagues and I discussed one hypothetical aspect of a death during anaesthesia recently. Should the anaesthetist remove a tracheal tube from the dead patient or should the tube be left *in situ* for the pathologist to identify its anatomical location?

The question was prompted by the declaration by a theatre sister that her standing orders required the tube should not be removed before postmortem examination. The conclusions that we came to were as follows.

There was no guarantee that a tracheal tube correctly located in theatre would still be so located after removal of the body to the mortuary.

Therefore, the postmortem identification of its location would not contribute to the determination of the cause of death.

The anaesthetist should ask a Consultant colleague to examine the body on the theatre table to confirm the location of the tube and to record this finding.

The anaesthetist should then remove the tube from the body.

West Cumberland Hospital, Whitehaven, Cumbria CA28 8JG D.M. Watson

Editor's note

This letter was shown to an anaesthetist who is a Coroner and to a Professor of Forensic Pathology for an expert view and it is published in order to clarify the legal position for our readers.

A legal opinion

In the event of a death during anaesthesia, it is far preferable to leave all apparatus *in situ* for the pathologist to examine, including all intravascular lines and anaesthetic intubation.

Where a tracheal tube is firmly held in place by ties or adhesive, there seems relatively little chance of it moving significantly from its original position. Neither should the cuff be deflated, as the condition of this may be important to examine. The older rubber cuff sometimes bulged over the end of the tube to block the lumen partly, although this is unlikely with modern devices.

Leaving the equipment in position by no means prevents an on-the-spot examination of the external visible parts by another anaesthetist, so long as the equipment is not removed.

Before the autopsy, there should always be a conference between the pathologist and the anaesthetist and, wherever possible, the latter or a colleague should attend the autopsy to confer again with the pathologist and satisfy himself as to the true situation. In the majority of anaesthesia-associated deaths it is the clinical and anaesthetic record and opinion that are paramount, but the pathologist has to discharge his duties at the behest of the Coroner and there seems nothing to gain by disturbing any evidence before he has the opportunity to examine it.

Institute of Pathology, Royal Infirmary, Cardiff CF2 1SZ B.H. Knight

Riversdale House, Merthyr Mawr Road, Bridgend, Glam. L.S. Addicott

Epidural anaesthesia for elective Caesarean section

We would like to comment on the recent article by Dr J.S. Crawford *et al.* (*Anaesthesia* 1986; **41:** 1039–46).

The authors recommend that prolongation of the interval between top-ups (incremental doses) is more important to safety than limitation of the total dose or dose rate. They also suggest that the incidence of hypotension may be reduced by prolonging the time to set up the epidural block. However, their data indicate that this technique may need multiple doses (up to nine) of local anaesthetic. Moreover, the dose of bupi-

vacaine exceeded 150 mg in 47% of their patients. There were five cases of serious bupivacaine toxicity.

In the last few years, the routine procedure at Queen Charlotte's Maternity Hospital has been to administer 20 ml 0.5% bupivacaine (100 mg) in a single dose fractionated over 5 minutes, with a further dose at least 20 minutes later if indicated. In our recent prospective series of 40 cases (submitted for publication), only 25% required further bupivacaine after the initial 100 mg. In only one case was a total dose of 150 mg exceeded. Our incidence of hypotension was greater than in the Birmingham series (27.5% compared to 14.4%) but no patient was hypotensive for more than 5 minutes.

Hypotension is a recognised complication that can be readily corrected by lateral position, further intravenous fluids and/or ephedrine, whereas bupivacaine toxicity is more hazardous and difficult to treat. We suggest, therefore, that the use of the incremental technique as reported by Dr Crawford and his colleagues is neither so effective nor so safe as the single dose administered slowly.

St Thomas' Hospital,
London SE1 7EH
Queen Charlotte's Maternity Hospital,
London W6 0XG

R.S. LAISHLEY
F. REYNOLDS
B.M. MORGAN

A reply

Thank you for the opportunity to reply to this letter, which merits serious consideration, not least because it identifies an interesting cleavage in what might be termed the philosophy of management of this procedure.

Firstly, the question of toxicity: it is somewhat disingenuous of your correspondents to make stark reference to our 'five cases of serious bupivacaine toxicity'. In four of those cases bupivacaine was administered in a concentration of 0.75% (and, in one of these, the injection was almost certainly inadvertently intravascular). This solution, however, has been abandoned for use in obstetric analgesia in this country because it is disappointingly ineffective, and because many of us realised that attempts to achieve a satisfactory spread of sensory blockade with 0.75%, invite a toxic response. Thus, we encountered one case of central nervous system toxicity among approximately 800 mothers who received the 0.5% solution, compared with four of the 173 for whom the 0.75% solution was used. This contrast alone surely demonstrates that, in respect to the potential of toxic response, the rate of administration is of greater importance than the total dose. Consideration of the 'bolus effect' applies not only to the contrast between intravascular and extravascular injection but also to the rapidity with which a high concentration is attained within the epidural space.

As regards the incidence of hypotension, again I believe that your correspondents have rather naughtily disguised their undoubted appreciation of the complete picture. It is true that our overall incidence of hypotension was 14.4%. However, our series extended from 1971 to 1985. As detailed in the text of our article, throughout the period 1978–85 (which included the time when 0.75% bupivacaine was in use) a vasopressor was required to reverse hypotension in only 5.5% of cases (which included an appreciable number of those in receipt of the 0.75% solution). The total incidence of hypotension during that period was 13.1%, and the condition was promptly corrected by a change of maternal posture and/or an increase in the rate of intravenous infusion in 7.6%. Your correspondents do not say in what proportion of their 27.5% of cases of hypotension, was a vasopressor agent given.

The impetus during the past few years in the practice of epidural analgesia for obstetrics, has been to reduce to a reasonable minimum the mass of drug administered with each injection and to observe that there are no dramatic ill-effects from that injection before another one is given. Indeed, that reflects one of the advantages which has prompted the increasing popularity of epidural infusions for labour (although I personally do not favour that technique, for other reasons). The same philosophy should surely be applied in regard to elective Caesarean section, otherwise we are on the retrograde path comparable to the dangers associated with spinal analgesia.

In our total series, 18.3% of mothers required five or more incremental doses and 16.2% needed no more than two, for a satisfactory block to be achieved. Thus, two-thirds needed three or four incremental doses given at intervals of approximately 15–20 minutes; the time that elapsed between first and final dose, therefore, was 40–60 minutes. This time, I believe to be well spent. If your correspondents have never found difficulty in safely attaining a sensory block that extends from T_4–T_6 to S_5 with one or two incremental injections, then I suggest that either they have been incredibly fortunate or they are vastly more adept at the procedure than any other anaesthetist to whom I have talked during the past few years. Certainly, the more protracted procedures can evoke ribald comment but we are neither harrassed nor harried by our obstetricians and midwives, who have plenty of other activities to engage them during the waiting time. Our patients are forewarned that the procedure of establishing a satisfactory block may take a considerable time, and are happy to know that we prefer safety to haste. The opinions expressed in the final sentence of your correspondents' letter do not, in my opinion, have the slightest validity.

Birmingham Maternity Hospital,
Birmingham B15 2TG

J.S. CRAWFORD

Obstetric epidural test doses

The evidence for the value of test doses with epidural anaesthesia has been fraught with illogicalities and anecdotes. The review by Prince and McGregor (*Anaesthesia* 1986; **41:** 1240–50) will help towards the development of a more consistent approach to their use. A few points remain conjectural and some of their recommendations are confusing.

Firstly, one would like to think that the test dose is necessary but the references quoted do not provide good evidence that the incidence of complications from epidural anaesthesia has been reduced since the advent of a particular test dose. These data are awaited patiently, perhaps from large series.

The aspiration test can fail from four major causes as described but, perhaps, a more common problem is the aspiration itself. Energetic suction causes an epidural vein to collapse over the catheter, which results in a false negative test for intravascular placement. It is more logical to hold the end of the catheter open to atmosphere, below its level of insertion into the patient, and observe any backflow of blood or cerebrospinal fluid.

Lignocaine does seem an ideal agent to test for accidental intrathecal placement. Preservative-free isobaric 2% lignocaine is widely available and gives rapid and consistent spinal anaesthesia in doses which vary from 20 to 80 mg.[1]

The authors imply that the responsibility for checking the position of the epidural catheter can be directed towards the midwives. Anaesthetists in most areas of the United Kingdom are fortunate to have the cooperation of midwives in the management of epidurals, but in how many centres are formal aspiration tests performed? Even if the midwives accepted the procedure it might not affect the complication rate, since the authors mention several causes of failure of the test (blockage, kinks, air locks with the filter). If one demands an aspiration test before each epidural top-up injection, then a further test dose should be applied each time, which would require that someone assessed the clinical effect of the test dose.

The interpretation of the test dose is difficult in obstetric patients but its misinterpretation is, perhaps, more significant than the authors suggest. For a 15-μg adrenaline test dose they quote that an intravascular injection is diagnosed if a 20% increase in heart rate occurs within 40 seconds of injection. About 12% of women in labour have an increase in heart rate of 30 beats/minute and 24% have an increase of 20 beats/minute after the injection of a *plain* epidural test dose.[2] That is, the false-positive rate is very significant compared to the low incidence of the complication for which the test is made. If the test dose criteria were followed strictly, then there might be much unnecessary re-insertion of epidural catheters.

Waterford Regional Hospital,
Ardkeen, Waterford, Ireland

P.D. CARTWRIGHT

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Accidental subdural catheterisation

We read with great interest the article by Lee and Dodd about an accidental subdural catheterisation (*Anaesthesia* 1986; **41:** 847–9). Previous cases, however, describe a fast onset of decreasing sense of temperature after a test dose of a local anaesthetic,[1] with no sensory or motor blockade, followed by partial or complete analgesia depending on the total anaesthetic dose given, without any marked effect on blood pressure.[2–4]

The patient described by Lee and Dodd showed no symptoms after a test dose of 6 ml lignocaine 1%, which suggests that an epidural injection occurred. However, an extended sensory blockade, without motor blockade, developed after the complete analgesic dose of bupivacaine 0.25%, which suggested subdural injection. This was confirmed radiologically and there was hypotension.

We conclude that the original catheter placement was in the epidural space. When the patient was repositioned the tip of the catheter migrated through the dura but not into the subarachnoidal space, causing a subdural blockade.

The tip of most epidural catheters is often quite sharp and rigid, so it is possible that this tip perforated the dura during movement of the patient and caused a subdural blockade. Many side-hole catheters are even sharper and therefore it is easier to breach the dura, although the catheter would have to travel further. The authors did not detect any vascular symptoms after 6 ml lignocaine 1% as a test dose; in our opinion, such a small dose without the addition of adrenaline, rarely causes any vascular symptoms.

Academisch Ziekenhuis,
Vrije Universiteit,
Amsterdam, The Netherlands

R. TREFFERS
J. J. DE LANGE

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A reply

Thank you for the opportunity to reply to Drs Treffers and de Lange. We read their case report with interest.

We consider their hypothesis to be incorrect, since almost all of the 3 cm of catheter inserted beyond the Tuohy needle would have had to migrate into the subdural space. It is unlikely that the almost purely subdural spread of contrast demonstrated in our radiograph, would have occurred had only one or two holes migrated subdurally.

We agree that 6 ml lignocaine 1% is too small a test dose. We routinely use 4 ml lignocaine 2% (80 mg) and recognise that this is not infallible; slow administration of the main dose is the main safety measure.

Royal Infirmary, A. LEE
Edinburgh EH3 9YW K.W. DODD

Failure of long-term epidural catheters

Tolerance to the drug is often assumed when epidural drug delivery becomes ineffective, either with local anaesthetic (as in child birth) or with opiates. This may not be the only explanation.

Forty patients had a tunnelled epidural catheter inserted for pain relief with either morphine or local anaesthetic. It became apparent during follow-up that, in some patients, the effectiveness of the system decreased suddenly, in some cases after a few hours, in others after some days after an initial period of use during which no technical problems were encountered.

We therefore decided to locate the catheters radiologically in a group of 25 patients as soon as this phenomenon became apparent. This occurred on 10 occasions: in two patients the catheter had come out of the epidural space, but in the other eight patients there was a failure of diffusion of the contrast agent into the epidural space associated with a sheath around the catheter, and sometimes reflux of the contrast medium. This observation was noted as early as 13 days and as late as 42 days after insertion of the catheter, and despite the use of various types of catheter material (polyvinyl, silicone). It occurred with both bolus injections and with infusions. An antibacterial filter was used in five of the 25 patients and a sheath around the catheter was noted in one of these five patients.

This phenomenon has been documented previously in animals[1–3] and suggested to occur in man.[4] It should be considered before sudden drug tolerance is invoked as the only explanation of sudden decreased efficacy. The mechanism of the phenomenon could be either a mechanical problem which leads to impaired diffusion due to fibrosis, or local metabolism due to inflammatory reaction caused by the presence of the catheter, or a combination of both these mechanisms.

Centre Hospitalier de Bicetre, L. BRASSEUR
94275 Kremlin Bicetre Cedex, J. BOURA
Paris, France A.-M. BRUNET
P. GABRIEL
C. BEGON
A. DESCORPS-DECLERE

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If nothing goes wrong—is everything alright?

In their article on cervical epidural anaesthesia in carotid artery surgery (*Anaesthesia* 1986; **41:** 1020–3), Dr Kainuma and his colleagues advocate the use of regional anaesthesia, particularly cervical epidural anaesthesia, as a safe and reasonable technique for the management of patients who require carotid artery surgery. Do their data support this suggestion? After 10 years' experience with cervical epidural anaesthesia in about 100 patients who suffered from chronic pain syndromes, the authors present an anecdotal report of three patients who underwent carotid artery surgery. From an anaesthetic point of view the patients were successfully managed. But does this mean that the technique is safe? Taking into account the authors' total experience with this technique there remains a statistical risk of a major complication that lies between 0 and 4.5%, with a confidence interval of 99%.[1] When 459 patients have been satisfactorily anaesthetised, then one can estimate the maximum risk to be less than 1%.

The greatest fear we would have with this anaesthetic technique is the risk of cervical compression from a small haematoma. From expert reports made for medical defence we know of two cases in which a thoracic epidural anaesthetic, that was performed *lege artis*, resulted in irreversible paraplegia. Both complications occurred in primarily healthy people. For anatomical reasons an epidural haematoma at the cervical or thoracic level leads to potentially more dangerous complications than at the lumbar level, where problems arise only when the haematoma is relatively large, and even when the lesion is confined to the lumbar and sacral segments only. In addition, our vascular surgeons use heparin during the operation, which makes the risk of bleeding even higher. Therefore, we consider a cervical epidural technique as too risky in this situation. However, even if it were known that the procedure definitely is safe, we have to discuss the second suggestion made by the authors: is cervical epidural anaesthesia reasonable in these patients?

Carotid artery surgery proceeded uneventfully in one patient, one patient suffered right hemiparesis despite immediate declamping and, in a further patient, surgery was discontinued because it was impossible to maintain consciousness during construction of a temporary bypass. Unfortunately, we are not told what happened further with this patient. Was he operated on later and, if so, what kind of anaesthetic was used and with what result? Of course, regional anaesthesia allows detection of an ischaemic insult earlier but does this infer that it alters prognosis? Test clamping in awake patients resulted in permanent neurological deficit not only in one of Dr Kainuma's patients but also in other patients reported in the literature.[2] Carotid artery surgery under regional block has been shown to result in comparable neurological morbidity but it has not been demonstrated convincingly that the non-neurological complication rate is definitely lower.[3–5] If this is true for regional block, there is no reason for cervical epidural anaesthesia to yield better results. Thus, on the surgical side we have no definite proof that regional anaesthesia is superior; and on the anaesthetic side the imminent risk of cervical epidural anaesthesia is greater than that of other anaesthetic techniques.

At a time where part of the medical community[6,7] is willing to banish halothane from further use because of the possibility of permanent hepatotoxic liver damage or even death, a risk that admittedly is very small indeed, one should seek for a comparable high standard in other fields of anaesthetic practice. We therefore see no place for cervical epidural anaesthesia for routine surgery of any type in the Western world.

University Hospital,
Josef-Schneider-Strasse 2,
D-8700 Wurzburg, FRG

M.J. Sold
K.H. Weis

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A reply

Thank you for giving us the opportunity to respond to the letter from Drs Sold and Weis.

There are indeed a number of reports which indicate that epidural haematoma is a complication of epidural anaesthesia when an anticoagulant is used during, or even after, epidural anaesthesia.[1,2] On the other hand, Rao and El-Etr[3] and Odoom and Sih[4] reported that epidural anaesthesia was performed safely in patients who received anticoagulant therapy. Hence controversy still exists about this.

Epidural haematoma is often associated with serious neurological damage; Stanley and Lunn[5] stated that it seems irrational to condemn the use of an epidural catheter in patients who receive anticoagulant therapy, when the lack of incriminating evidence is considered. Firstly, the incidence of epidural haematoma formation in patients with epidural catheters who are subsequently given anticoagulant, is unknown. Secondly, since spontaneous epidural haematoma formation is a well-recognised complication of any form of anticoagulant therapy, it is possible that the presence of a catheter in the epidural space at the time of anticoagulation has little to do with the subsequent formation of epidural haematoma. Thirdly, no data are available to indicate that the incidence of haematoma formation is any greater in patients with a catheter in their epidural space who are given anticoagulants.

Therefore, we consider that the 'greatest fear' that Drs Sold and Weis had with this technique is not sufficient to contraindicate the use of cervical epidural anaesthesia in carotid artery surgery, whose advantages we describe in our article. Nevertheless, we must emphasise the following points so that this procedure is truly safe and reasonable. Firstly, the epidural catheter must be inserted gently and must be removed if the introduction of the catheter results in a traumatic tap.

The use of fluoroscopy prevents the need for repetitive attempts at catheter insertion and decreases the rate of traumatic taps. Secondly, administration of heparin must be monitored with activated clotting time (ACT) throughout the surgery: the dose of heparin should be regulated to keep ACT below 200 seconds. Heparin activity should be neutralised before the epidural catheter is removed. Thirdly, neurological examination must be performed at regular intervals postoperatively so that epidural haematoma may be diagnosed and treated promptly.

Of patients who undergo carotid endarterectomy, 10–20% do not tolerate cross clamping of the carotid artery, depending on the degree of involvement of the other vessels, collateral circulation and the anatomy of the circle of Willis.[6] The obvious advantages of regional anaesthesia, including cervical epidural anaesthesia, consist in earlier detection and therapy of neurological insult, and test clamping to identify those patients who need an indwelling shunt. Unconsciousness occurs 10–20 seconds after cessation of cerebral blood flow and irreversible brain injury starts in 5 minutes, due to depletion of glucose and ATP stores.[7] This is the point of the 5 minutes needed to detect and treat the ischaemic insult. We consider that this is more reliably done in a conscious patient under regional anaesthesia. If the insult is thus diagnosed as due to an embolus, the surgical procedure can be modified immediately to prevent its aggravation. Test clamping has obvious advantages over the insertion of a shunt, since only 10% of patients who undergo carotid endarterectomy are reported to require a shunt.[8] Insertion of the shunt may produce microembolisation or disruption of the posterior intima, and require longer arteriotomy.

Neurological deficit in our patients could never be evidence to condemn test clamping, and these patients could have had an increase in their neurological deficit from insufficient cerebral blood flow if we had not known their syncopal attacks with test clamping. The third patient had no permanent neurological deficit postoperatively and was not operated on later.

The incidence of non-neurological complications under regional anaesthesia was reported to be much lower than under general anaesthesia in Peitzman's article[8] to which Dr Sold and his colleague referred. Therefore, there are no grounds to support their assertion.

We agree with them that if nothing goes wrong it does not mean that everything is alright, and that one should seek for a comparable high standard technique with smaller risk. We again insist that cervical epidural anaesthesia is a preferable technique in patients at high risk for carotid artery surgery in order to protect their brain and non-neurological organs with smaller risk and higher reliability, when a skilled anaesthetist performs this technique.

Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan

M. Kainuma
Y. Shimada

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Graseby PCAS pumps—a potential hazard

We recently experienced a problem with a new Graseby patient-controlled analgesia system (PCAS) pump which revealed two potential hazards.

A patient was connected to the pump postoperatively after detailed instructions pre-operatively by an experienced research nurse. The pump was set according to the manufacturer's instructions and a bolus dose of 2 mg morphine, a background infusion of 2 mg/hour and a lock-out time of 10 minutes were selected. The key was removed from the pump to prevent unauthorised adjustment. One hour later the patient was found to be very drowsy and attempts at adjustment of the pump were unsuccessful, since none of the controls, including the stop button, was operative. The key was used to turn the pump off and it was then found that the patient had the button on the handset depressed constantly. The patient was disconnected from the pump and made an uneventful recovery.

Evaluation in the laboratory showed that only a very slight depression of the handset button was necessary to trigger a demand. The connexion between the handset and the pump is pneumatic. A pressure of 2 kPa was adequate to trigger a demand

against a maximum of 16 kPa at full depression of the handset button. Furthermore, there was no diminution of that pressure no matter how long the handset button was depressed. If the handset button was depressed continuously the controls became inactive and a bolus dose was administered at the end of every lock-out period.

The philosophy of patient-controlled analgesia (PCA) is that the patient *consciously* demands analgesia as he/she requires within the limits of the maximum dose set by the user. If our pump is representative, it is clearly possible for the present Graseby PCAS pumps to administer bolus doses which the patient has not *consciously* demanded. A further hazard is that, in the absence of the key, administration can be stopped only by disconnexion of the patient from the pump should the handset button stick or be held in the depressed position.

PCA pumps should respond only to conscious demands from the patient and it should be ensured that the demand button is pressed rapidly (in this case by introducing a leak in the pneumatic system) or twice in quick succession. The latter method was used most successfully in the Cardiff Palliators which are the predecessors of the present PCAS pumps, and is probably the safest since other, similar pumps have also been noted to be capable of administering non-requested doses.[1] It would be helpful if a consensus could be reached on the optimum method to ensure that PCA pumps do not deliver unwanted doses of analgesic drugs.

The General Hospital,
Leicester LE5 4PW

C.D. HANNING
B. OGDEN
P. PARRY

Reference

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A reply

Our detailed investigation of the event described in this letter led us to the conclusion that the patient concerned depressed the demand button to a position that corresponds to the operating point of the pressure-actuated electric switch. This caused the switch to go on–off–on repeatedly.

We shall introduce a product modification which avoids this possibility and also allows operation of the front panel controls whilst the demand button is held depressed.

Graseby Medical Ltd,
Watford,
Herts. WD2 4LG

T.J. COOMBS

Sampling for carbon dioxide

We read with interest the letter by Drs Machin and MacNeil (*Anaesthesia* 1986; **41:** 971–2) which described a modified angle piece for sampling gas from the under-mask space.

The close correlation between vapour concentrations measured at the proximal and distal ends of the tracheal tube is widely accepted[1–5] and was confirmed to our satisfaction in a sequence of studies conducted in this department 2 years ago. One infrared analyser (Beckmann LB2) recorded the values obtained from one of the sampling ports in the modified tracheal swivel mount, which we have described,[6] while a second infrared analyser recorded the values obtained from a 6-F.G. infant feeding tube attached to a second sampling port and advanced to the distal end of the tracheal tube (Fig. 1). In a further stage of this study, using the same analysers, end tidal values recorded from the proximal end of the tracheal tube were compared with values recorded from the under-mask space. For this purpose the children were anaesthetised with halothane, nitrous oxide and oxygen and, when spontaneous ventilation had been established for 20

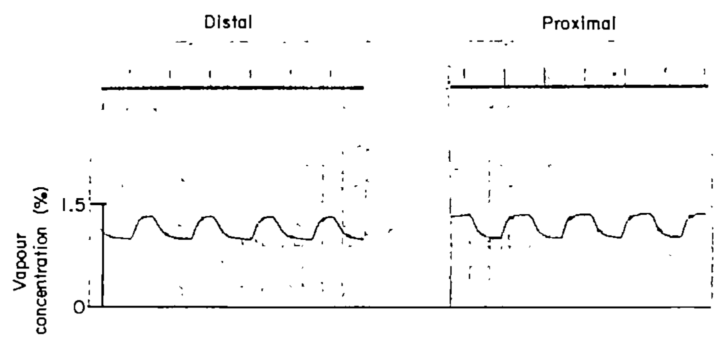

Fig. 1. Beckmann LB2 recordings from distal and proximal ends of tracheal tube. IPPV, f = 40 breaths/minute, I:E = 1:2.

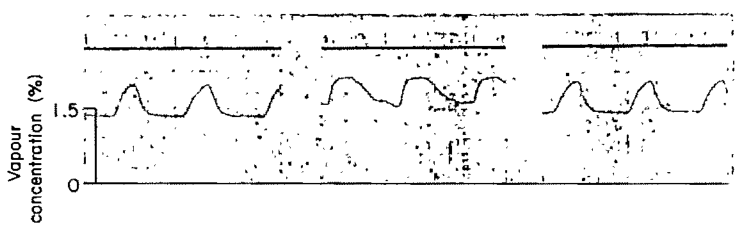

Fig. 2. Beckmann LB2 recordings from tracheal tube and mask. $f = 20$ breaths/minute, I:E = 1:2.

minutes, end tidal halothane values were recorded from the modified swivel mount inserted into the facemask. Following tracheal intubation the swivel mount was attached to the proximal end of the tracheal tube and, after spontaneous ventilation with the same vaporizer halothane concentration for a further 15 minutes, end tidal values were recorded from the proximal end of the tube. The children were then extubated, anaesthesia was continued with a facemask and, following a further 15 minutes of spontaneous ventilation, end tidal values were again recorded.

The results of this study (Fig. 2) clearly failed to show agreement between under-mask samples and values recorded from the proximal end of the tracheal tube, and thereby confirmed Severinghaus' observation[7] that 'the gas under a mask is not suitable for collection of end-tidal samples', which must also be applied to the technique proposed by Drs Machin and MacNeil.

Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Eire

P. ALLEN
W.S. WREN

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Cold injury and hyperkalaemia

Drs Laycock and Loughman (*Anaesthesia* 1986; **41:** 739–41) present the intriguing possibility that cold injury may be associated with suxamethonium-induced hyperkalaemia. The mechanism that underlies this response, is thought to be an increase in extrajunctional acetylcholine receptors.[1] In the case reported it is possible that other factors may have led to the increase in receptors. The authors do not state if muscle relaxants were administered to their ventilated patient. There is evidence that chronic administration of non-depolarising relaxants[2] or even immobilisation alone[3] may, by themselves, increase receptor numbers. Further work is necessary before cold injury can be confirmed as the culprit. As a final comment, the authors raise the possibility of danger with suxamethonium in patients after hypothermic circulatory arrest or cold injury from exposure or immersion. In the case described, as in all others,[1] there is a delay of several days after the injury before the danger exists. In the recently hypothermic patient, on present evidence, suxamethonium is not contraindicated.

Massachussetts General Hospital, Boston, MA 02114, USA

J.A.J. MARTYN

Hospital for Sick Children, Great Ormond Street, London WC1N 3BR

D.R. GOLDHILL

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Plasma hormone measurements following midazolam administration

We were interested to read the excellent paper by Drs Dawson and Sear (*Anaesthesia* 1986; **41**: 268–71) since it confirms our earlier finding that induction of anaesthesia with midazolam did not significantly alter the plasma cortisol[1] or thyroxine levels although the prolactin level was slightly increased at the beginning of surgery. The cortisol and prolactin concentrations were increased appreciably at the end of operation and after surgery. Twenty-four hours later the hormone levels returned to the pre-induction values (Table 1). In this study 0.3 mg/kg midazolam and 4.4 μg/kg fentanyl were administered for induction of anaesthesia.

We would like to report briefly on our findings concerning the ACTH, cortisol, prolactin, thyroxine and tri-iodothyronine changes in women after intravenous administration of 0.3 mg/kg midazolam. Blood samples were taken before and 10 and 20 minutes after administration of midazolam. Surgery was started following this 20-minute period. The plasma hormones were measured by radioimmunoassay. The results did not reveal significant changes in plasma hormone levels (Table 2).

We hope that these results may help to clarify the anaesthetic-induced neuroendocrine changes and their stress-reducing effect.

6726 Szeged,
Alsokikoto sor 6,
Hungary

A. Kertész

Reference

1. Kertész A, Falkay G, Boros M. The effects of benzodiazepines as anaesthesia inducing agents on plasma cortisol level in elective hysterectomy. *Acta Medica Hungarica* 1985; **42**: 145–52.

Table 1. Mean (SEM) plasma cortisol, prolactin and thyroxine levels during and after hysterectomy.

Blood samples ($n = 11$)	Cortisol, nmol/litre	Prolactin, mU/litre	Thryoxine, nmol/litre
Before induction	381.1 (49.2)	549.7 (75.6)	140.9 (5.8)
After intubation	367.8 (48.3)	982.8 (123.5)*	130.9 (4.4)
Five minutes after skin incision	387.2 (60.4)	2937.1 (290.6)**	131.2 (6.0)
End of surgery	680.2 (51.7)*	3411.1 (421.5)**	136.8 (5.1)
Two hours after surgery	825.4 (129.0)*	1684.8 (201.8)**	135.9 (6.2)
Eight hours after surgery	656.0 (72.7)	675.0 (87.6)	151.7 (4.1)
Twenty-four hours after surgery	435.4 (44.4)	543.9 (80.9)	134.3 (3.5)

* $p < 0.01$. ** $p < 0.001$.

Table 2. Mean (SEM) plasma ACTH, cortisol, prolactin, thyroxine and tri-iodothyronine levels during induction of anaesthesia with midazolam.

Hormones	Before administration of midazolam	Ten minutes later	Twenty minutes later
ACTH, pg/ml	96.2 (11.9)	85.3 (20.1)	75.6 (14.5)
Cortisol, nmol/litre	515.8 (82.2)	484.4 (98.4)	470.6 (106.2)
Prolactin, mU/litre	327.8 (65.4)	387.0 (73.8)	475.8 (89.6)
Thyroxine, nmol/litre	123.8 (8.5)	106.1 (11.5)	112.9 (11.7)
Tri-iodothyronine, nmol/litre	2.0 (0.04)	2.0 (0.08)	2.2 (0.06)

Guide-wire assisted arterial cannulation—a complication

Guide wires are established as a safe and reliable method to assist intravascular cannulation.[1] This letter describes a potentially serious complication which involved guide-wire assisted intra-arterial cannulation.

Attempts were made to cannulate percutaneously one of a patient's radial arteries. This was impossible and a 20-gauge Teflon catheter (Quick-Cath) was inserted into the right brachial artery. Adequate backflow was observed. On connexion of the cannula to a pressure transducer the waveform was of poor quality, although backflow was still present. Bending of the tip of the catheter was suspected and an attempt was made to introduce a guide wire to facilitate a larger diameter cannula. The guide wire (Arrow Positive Placement Spring wire guide RW-04018) was introduced without difficulty and, after the other end of the guide wire had been disconnected from its plastic introducer kit, the 20-gauge cannula was removed and an unsuccessful attempt made to insert another cannula over the guide wire. We decided to abandon cannulation at this site; however, removal of the guide wire proved difficult. Further examination of the wire, once removed, revealed considerable stretching and uncoiling of the outer coating so that its length was almost doubled. A femoral artery catheter was inserted for arterial pressure monitoring. No sequelae of arterial damage were noted postoperatively.

For the safe use of guide wires it is necessary to

understand their design.[2] Guide wires consist of a central mandril with an outer flexible helix. The wire's integrity is maintained by a weld of the components together at the ends of the mandril. Previous reports have attributed difficulty in removing guide wires to arterial spasm[3] or to kinking of the wire.[4] In our case, the integrity of the wire was disrupted on disconnexion from the plastic introducer kit and, as a result, the coil could separate. If inadvertently misplaced within the vessel wall, this could increase the likelihood of fixation to tissue, with consequent difficulty in removal. When a guide-wire technique is used for intravascular cannulation, it is essential closely to observe manufacturers' instructions about their use and to avoid any action which is liable to disrupt the integrity of the wire.

Royal Infirmary, I.M. McMenemin
8–16 Alexandra Parade, G.N.C. Kenny
Glasgow G31 2ER

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A reply

It clearly behoves the user, as Drs McMenemin and Kenny point out, to follow the manufacturer's instructions regarding the use of any device. In particular, the case presented involves the use of a spring wire guide and plastic introducer designed to facilitate insertion of an arterial catheter. Its construction consists of a 0.018", straight, soft-tip spring wire guide bonded to a plastic actuating lever. The entire unit is encased in a plastic introducer or feed tube. The idea behind the design is that when a difficult arterial cannulation presents itself, the spring wire introducer assembly can be attached to the hub of the introducer needle. When backflow or flashback is received, the spring wire is advanced, using the bonded actuating lever, through the lumen of the introducer needle. At this point the tip of the arterial catheter is within the lumen of the artery and the spring wire guide, as it is advanced, will track the vessel. Once the spring wire is within the artery, the arterial cannula is slipped off the introducer needle and follows the path of the guide wire. Completion of the cannulation requires removal of the introducer needle and spring wire assembly as a unit. At no time is the spring wire guide disconnected from its plastic introducer, nor should the spring wire guide be withdrawn back through the introducer needle.

This guide wire assembly was not designed for a catheter exchange. The suggested procedure does not compromise the integrity of the spring wire guide. Individually packaged straight soft-tipped wires are manufactured and designed for this application.

Arrow International re-iterate the statement of Drs McMenemin and Kenny; it is essential closely to observe manufacturer's instructions. Arrow International put a lot of time and effort into writing clear and concise instructions for the use of their products. In addition, since Arrow International design products to be safe, effective and convenient, reading the instructions will be mutually beneficial to both user and patient.

If questions still remain about the intended use of a product, we can always be contacted directly for answers.

Arrow International, Inc., P.J. McGregor
P.O. Box 6306,
Reading,
PA 19610, USA

Drilled for safety

The problem of over-pressure in breathing systems is still with us. Neither high- nor low-pressure relief outlets are satisfactory when the same system may be required in both controlled and spontaneous ventilation. Alternative methods have been devised, such as a secondary spring in the expiratory valve or a reservoir bag outlet, but a relief hole in the system may be all that is needed. The inflating valve of the Cardiff infant resuscitator (Penlon Ltd) uses a pin-hole leak to avoid prolonged pressures. We have tried a similar solution for the variable-orifice device described previously (*Anaesthesia* 1979; **34:** 686). The flow-controlled expiratory valve now has a 1-mm diameter hole drilled through the 35-mm long tapered screw (Fig. 1). Sur-

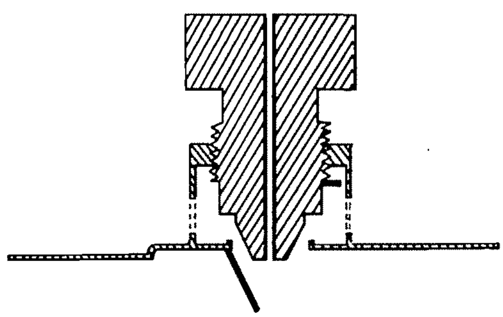

Fig. 1. Part of valve to show relief vent.

prisingly, when closed it will vent an anaesthetic gas mixture of nitrous oxide 6 litres/minute and oxygen 3 litres/minute with an increased pressure difference of only 0.7 kPa. No air is entrained during normal use with a Magill attachment and losses are negligible through a narrow bore of this length. The leak port is occluded easily for positive pressure ventilation if necessary. The system cannot be over-pressurised at conventional flow rates and there is no possibility of a safety valve malfunction.

Royal West Sussex Hospital,
St Richard's,
Chichester PO19 4SE

M.R. NOTT

An unusual cause of complete expiratory obstruction

This is a report of an unusual cause of blockage to the expiratory part of a Bain coaxial breathing attachment (Mediplast). Complete expiratory obstruction became apparent during the first case on a morning operating list, and was found to be due to a grey rubber bottle-top (later identified as belonging to a 0.5-G 'Intraval Sodium' container, Fig. 1) which was firmly jammed across the scavenging outlet of the expiratory valve (Fig. 2). It seems likely that the rubber bung was dropped on the floor near the anaesthetic machine during the previous day, picked up by a helpful cleaner during the evening and inserted into the nearest suitable-looking hole, which happened to be of precisely the right size. The cause of the blockage was recognised promptly and removed, with some difficulty, with the aid of an artery forceps. My usual 'cockpit drill' had not detected the problem and, although the patient came to no harm, the incident is a salutary reminder that in anaesthesia, whatever precautions may be taken, the unexpected can always occur.

The General Infirmary,
Leeds LS1 3EX

T.M. JACK

Fig. 1.

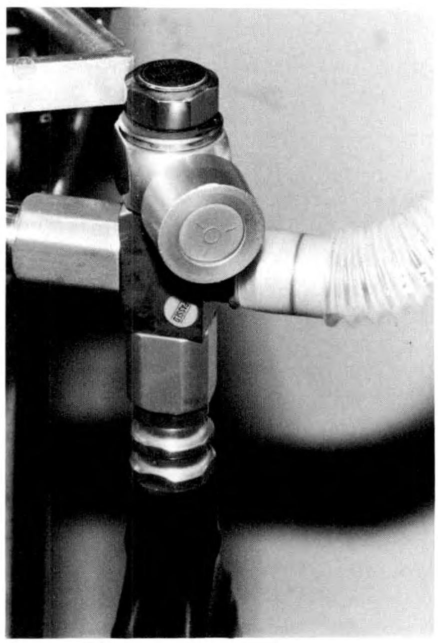

Fig. 2.

The spasm of the sphincter of Oddi can be avoided

K.J. Bird once again draws your readers' attention to the fact that narcotic analgesics may cause spasm of the sphincter of Oddi (*Anaesthesia* 1986; **41:** 1120–3). This effect of the narcotics can be seen not only during intra-operative cholangiography, when the spasm may lead to misinterpretation of the X ray picture and, perhaps, to a wrong diagnosis of impacted common bile stones, with needless exploration of the common bile duct, but also when opiates are used for premedication in the patient for non-biliary surgery.

We started 3 years ago to use nalbuphine (Nubain ®) for analgesia during extrahepatic biliary tree surgery.[1] In our practice, this synthetic opiate agonist–antagonist never increased the common bile duct pressure and, on many occasions, even decreased it. We also found that nalbuphine can be used efficiently for postoperative analgesia in patients after cholecystectomy and choledochotomy without spasmogenic effect on the sphincter of Oddi.[2]

Thus, we now use nalbuphine at all stages of the patient's treatment in biliary surgery, or for non-biliary surgery in patients with biliary or pancreatic disorders.

Hadassah University Hospital,
Mt Scopus,
Jerusalem 93240, Israel

E. VATASHSKY
Y. HASKEL

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Oculogyric crisis after day case anaesthesia

Antiemetics are often administered at the induction of anaesthesia to avoid some of the minor morbidity problems which are common in day case gynaecological patients. Low dose droperidol, when used in association with opiates, is useful for both antiemesis and for decreasing postoperative discomfort in patients since the long action of this drug is an advantage.[1,2] The following is a report of an oculogyric crisis which occurred in a day case gynaecological patient after an anaesthetic technique which included low dose droperidol, alfentanil and intermittent propofol.

A fit, 55-year-old Indian female with a history of menorrhagia presented for dilatation and curettage. She had previously undergone three Caesarean sections (India, 1962, 1972 and England, 1965) when she had suffered from postoperative vomiting. Her weight was estimated at 45 kg and her haemoglobin was 13.3 g/dl.

Induction was commenced with droperidol 2.5 mg and alfentanil 250 μg followed by propofol 9.5 mg/ml with 0.5 mg lignocaine/ml until sleep occurred (8 ml in total). Transient apnoea reverted to normal spontaneous ventilation within 30 seconds and a 40% oxygen in nitrous oxide mixture was administered. A further 2 ml of propofol was given before the patient was positioned for lithotomy and the dilatation and curettage were completed without incident.

Recovery was in the left lateral position with 100% oxygen given via a facemask. Observations remained stable but the patient remained unresponsive to verbal command after 10 minutes in the recovery ward. She started to grimace 20 minutes after return to the recovery area followed within 15 minutes by violent writhing and opisthotonos.

The patient was unresponsive with marked extrapyramidal movements but there were no focal neurological signs. Blood pressure, pulse, ECG, full blood count and serum electrolytes and glucose were within normal limits. In the absence of other precipitating factors this was assumed to be secondary to the anaesthetic agents. Procyclidine 10 mg intravenously was given to decrease the severity of movement and, when this failed, the patient was later sedated to avoid possible injury.

This had little effect and, to prevent any distress or risk of injury to the patient, she was sedated with a chlormethiazole infusion and admitted to the medical wards for observation. The infusion was gradually decreased and the patient was lucid and orientated within 48 hours. All subsequent investigations, including an EEG and brain scan, were normal and the patient was discharged 6 days later.

Other causal factors for a central nervous system disturbance in a previously normal patient were excluded, namely hypoxia (especially important in dark-skinned patients), previous or present epilepsy, hypoglycaemia or cardiovascular disturbances, before the diagnosis of oculogyric crisis was assumed.

Droperidol has extrapyramidal side effects but there is little to suggest this could occur with low dosage. There have been no reports of extrapyramidal effects with either alfentanil or propofol.[3] It is likely that these effects were due to droperidol but one cannot identify the causal agent definitely when other drugs are used unless the patient is re-exposed to each individual drug, but she was reluctant to undergo this procedure. She has been issued with a warning card which names the three agents used and describes the reaction that ensued, so that drugs with a similar central action may be avoided in the future.

Stepping Hill Hospital,
Stockport SK2 7JE

A.E. DINGWALL

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Action of narcotics on the pupil

The miotic effects of narcotics are probably brought about by removal of inhibition at the pupilloconstrictor nucleus but direct effects upon the pupillary sphincter are also possible.[1] Opioid receptors are present in the eye of many species and topical morphine can constrict the human pupil.[2] If intravenous narcotics act on the human pupil partly through ocular receptors, then their effects should also be apparent in patients with brain death. With the approval of the Institutional Review Committee of the French Hospital, two patients with brain death[3] were administered intravenous narcotics just before respiratory support was terminated. Both patients were noted to have normal pupillary reactions before death and were not hypothermic or on anticholinergic medication. Pupil size was measured by both infrared (Pupilscan; Fairview Medical Optics, Inc., Amersham, Bucks.) and photographic pupillometry. The first patient was an 80-year-old, 52-kg woman who developed brain death during cardiopulmonary resuscitation. She was maintained on a 10 μg/kg/minute dopamine infusion and continuous mechanical ventilation. Her pupils were 6.2 mm bilaterally and did not change in size for the 20 minutes of measurement after 10 mg intravenous morphine. The second patient was a 41-year-old, 46-kg woman who developed brain death secondary to a ruptured cerebral aneurysm. Fentanyl 250 μg was given as a bolus following removal of her kidneys, and her pupils were observed for 10 minutes before the ventilator was turned off. Dopamine 5 μg/mg/minute was discontinued after the skin incision, 25 minutes before administration of fentanyl. Prior to fentanyl her pupils were 6.0 mm bilaterally and they did not change in size after the drug. These observations suggest that in humans, as described with dogs,[4] the brain is necessary for the development of miosis following intravenous narcotics. Ocular mechanisms that contribute to miosis must consequently be negligible.

French Hospital,
P.O. Box 7883,
San Francisco,
CA 94118, USA

M.D. LARSON

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Loading frame for pneumatic pressure infusor

Various modifications to the fabric type of pressure infusor have been suggested, including the use of a tourniquet inflator to assist inflation[1] and suction to hasten deflation.[2] Insertion of the bag of fluid into the infusor, however, remains cumbersome. The simple loading frame described herein facilitates bag changing and has been found to be of considerable value in situations where multiple rapid blood transfusion is required. The infusor used is a commercially available type constructed of synthetic fabric* which imparts an intrinsic rigidity to the infusor.

The frame is constructed of aluminium tube mounted on a block which is attached to a standard drip-stand such that the frame is in the vertical plane but standing proud of the drip-stand by 5 cm (Fig. 1). A deflated infusor can thus pass over the frame (Fig. 2). The bag of fluid is hung from a wide-based hook fixed to the bottom of the frame. This wide hook serves to align the bag in the correct plane and prevents the bag from twisting around; it also serves to hold the deflated infusor in the up position.

It is a simple manoeuvre to lower the deflated infusor over the bag. A cord of appropriate length connects the infusor to the block of the frame. This limits the fall of the infusor so that, in the down position, the infusor sits correctly over the bag (Fig. 1). The pressure gauge has been removed from the bag and mounted on the block of the frame so that the infusor hangs centrally on the frame.

Rapid deflation, without using suction, is achieved by simple modifications to the pipework with the introduction of a wide-bore T-piece adjacent to the infusor. Release of a clip on the exhaust limb of this T-piece permits rapid deflation, provided that the plastic nipple on the infusor is cut back 0.1 cm to widen its exit diameter. Deflation is entirely via this route; the bleed valve remains closed throughout. Inflation is achieved using the standard inflating bulb. A bag change cycle (deflation, change bag, inflate to 300 mmHg) is accomplished in approximately 35 seconds.

* 'Prescuf 500', Medical-Assist Ltd, Commerce Way, Whitehall Industrial Estate, Colchester, Essex.

Fig. 1.

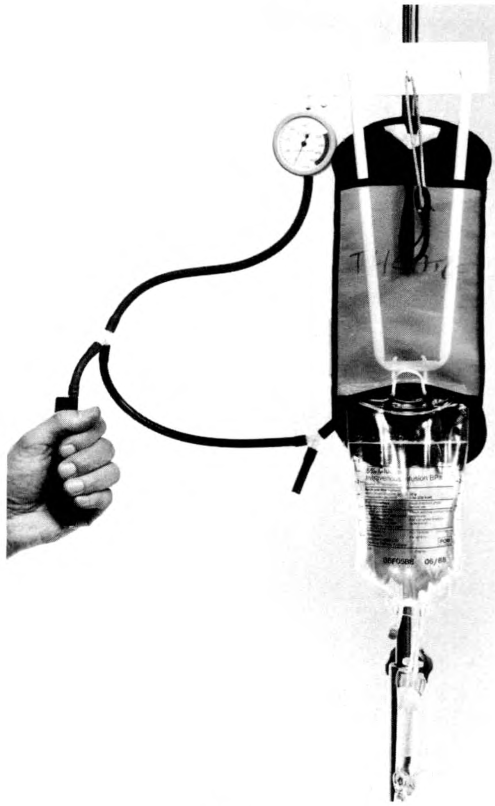

Fig. 2.

Commercial enquiries should be made to H.G. Wallace Ltd, Whitehall Road, Colchester CO2 8JH.

Frenchay Hospital,
Bristol BS16 1LE

I. NORLEY

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Difficult bronchial intubation

May I add to the recent correspondence on difficult bronchial intubation? The use of various bronchoscopes is effective but perhaps simple manoeuvres are more desirable.

In my practice I have found that manual displacement of the trachea away from the side to be intubated, after the tube is placed in the upper trachea, is frequently effective. Presumably, this alters the angles around the carina, and that of the approaching tube, sufficiently to tip the tube into the appropriate bronchus.

Whiston Hospital,
Prescot,
Merseyside

A.C. SKINNER

Buprenorphine, benzodiazepines and prolonged respiratory depression

A 50-year-old male patient presented for cystoscopy and optical urethrotomy under general anaesthesia. His past medical history revealed that he had received two uneventful general anaesthetics for anterior spinal fusion at the L_5/S_1 level in February 1982 and for posterior lateral spinal fusion at the same level in March 1986.

He was on buprenorphine 0.2 mg sublingually 6-hourly, paracetamol 1 g 4–6-hourly and nitrazepam 10 mg *nocte* when required for his backache. He was seen

by one of the authors (M.S.) at 17:30 hours on the day before the operation and was prescribed temazepam 20 mg orally to be given 2 hours pre-operatively.

The patient, who weighed 60 kg, arrived in the anaesthetic room at 15:00 hours and anaesthesia was induced with a sleep dose of thiopentone 300 mg and maintained with oxygen 33% in nitrous oxide and enflurane, via a facemask and Magill breathing system. He was noticed to have a bradypnoea of 3 breaths/minute immediately after induction. Therefore, ventilation was assisted manually between the patient's own breaths to avoid hyperventilation. Enflurane was decreased to 0.8% but the patient continued to breathe at 3 breaths/minute.

The cystoscope was introduced at this stage and this produced no change in the heart or respiratory rate. Re-examination of his medication chart revealed that the patient had received sublingual buprenorphine 0.2 mg for his backache at 22:30 hours on the previous night, 0.4 mg at 06:30 hours and 0.4 mg at 11:55 hours on the day of the operation: a total of 1.0 mg over a period of 16.5 hours, from the time of the first dose of buprenorphine to induction of anaesthesia.

Doxapram, in 20 mg boluses to a total of 60 mg, was administered to bring his respiratory rate to 10 breaths/minute. The operation was completed by then and the patient was taken to the recovery room where he remained drowsy but rousable. His respiratory rate decreased to 6 breaths/minute as soon as he was left undisturbed. Therefore, a doxapram infusion was set up and continued overnight. The rate of infusion was adjusted to maintain the respiratory rate greater than 12 breaths/minute. The following morning the infusion was discontinued without further problems.

There have been a few reports in the literature[1-3] about prolonged somnolence and respiratory depression following a combination of oral long-acting benzodiazepines (lorazepam or diazepam) and intravenous buprenorphine under general anaesthesia. Green,[4] however, reported no incidence of respiratory depression when intravenous buprenorphine was combined with short-acting benzodiazepines and a short-acting induction agent.

Buprenorphine is now prescribed more frequently by general practitioners and it is not uncommon to be confronted with patients who present for a general anaesthetic and who already receive sublingual buprenorphine for some other ailment. Our case illustrates that buprenorphine administered sublingually not as part of an anaesthetic, but as an analgesic, can lead to prolonged somnolence and respiratory depression when combined with a short-acting benzodiazepine under general anaesthesia.

Ysbyty Gwynedd,
Bangor,
Gwynedd LL57 2PW

M. SEKAR
T.J. MIMPRISS

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Spontaneous ventilation in old people

This is to thank Dr T.H.S. Burns for his letter (*Anaesthesia* 1987; **42:** 76). Some of the points that he makes about halothane have been made elsewhere and have probably been debated fully.[1] The point I wish to make, is to agree with him wholeheartedly about the preference for spontaneous ventilation in elderly patients with fractures. Since in the past I have had some difficulty in getting them to breathe again after either paralysis or intravenous narcotics or both, despite great care, I now allow them to breathe spontaneously. The ultimate compliment on this technique was paid to me by the recovery room staff who, after I had done some five or six, commented on how much better the patients were.

Sadly, many trainees have been subjected to forceful propaganda by the advocates of ventilation, intravenous agents and regional block. It is the last named that has particularly exercised me. Many people are put through the extreme discomfort of epidural blocks which are performed when the patient lies on the side of the fracture. Certain respiratory cripples may require subarachnoid block but they can be sat up, which is not quite as distressing as lying on a fracture. If the advocates of regional anaesthesia, particularly for hip fractures, thought through the potential problems, such as access, variable spread and toxicity of the agents, a more logical viewpoint could be given to trainees. Since old people, by definition, need very little in the way of anaesthetic agents, I would wholeheartedly advocate that small quantities of volatile agents given to patients who breathe spontaneously, is the ideal solution.

Manchester Royal Infirmary,
Manchester M13 9WL

R.I. KEEN

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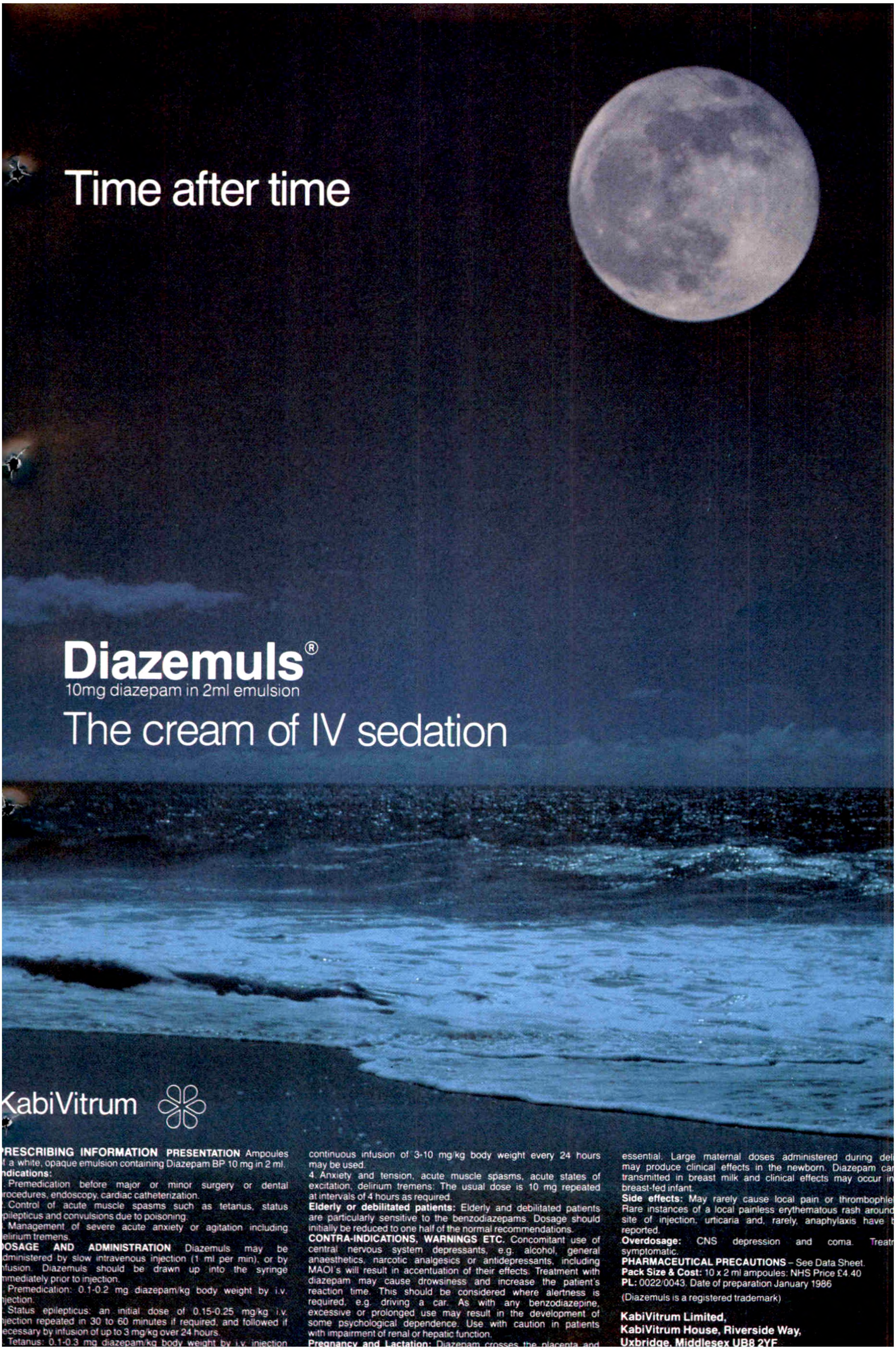
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continuous infusion of 3-10 mg/kg body weight every 24 hours may be used.
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Elderly or debilitated patients: Elderly and debilitated patients are particularly sensitive to the benzodiazepams. Dosage should initially be reduced to one half of the normal recommendations.
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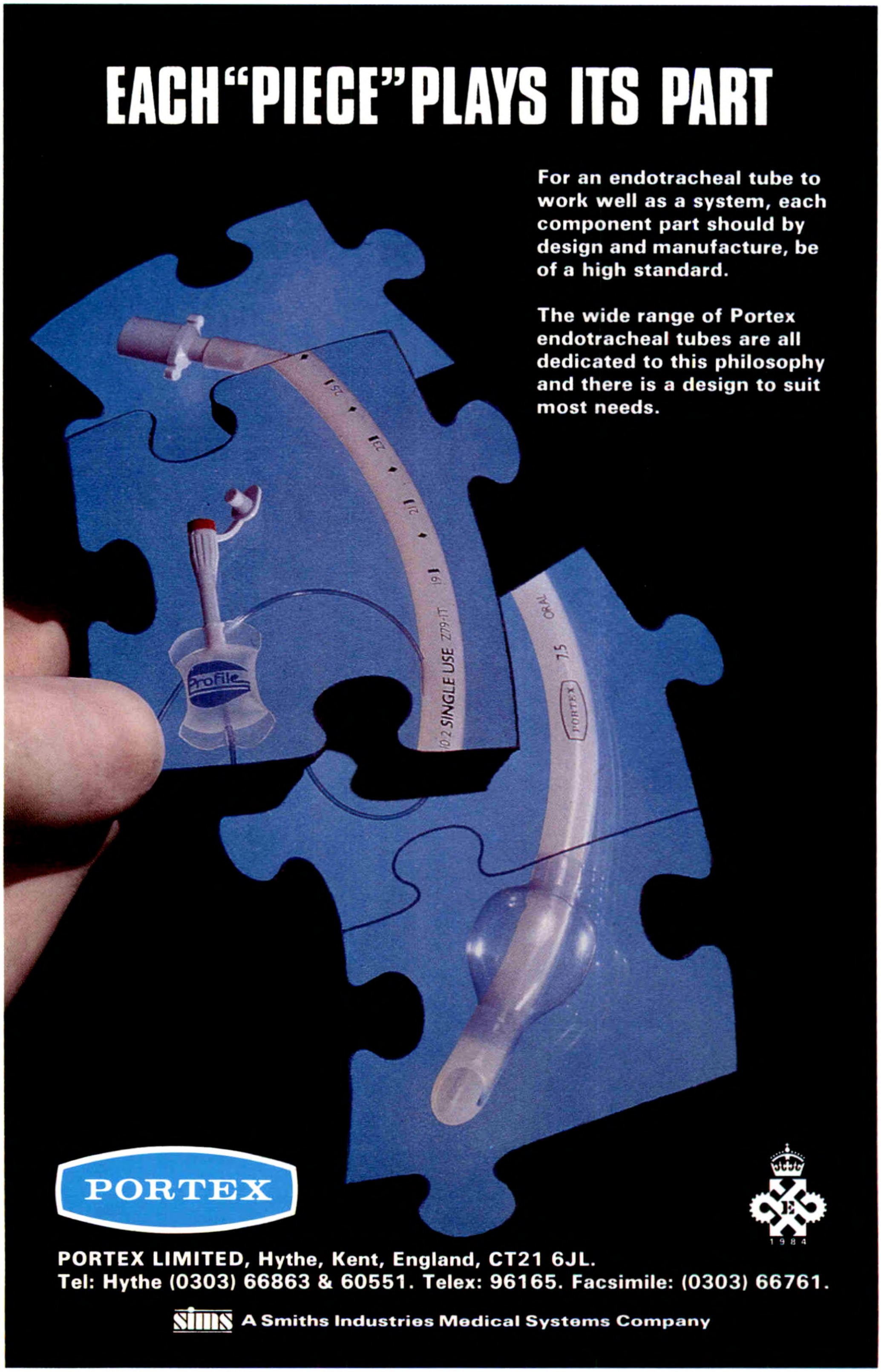
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Smoking and anaesthesia

The recent editorial (*Anaesthesia* 1987; **42:** 1–2) was very interesting since for over a year I, with one of my surgical colleagues, have sent a letter to all patients who are booked for elective surgery. This informs patients who smoke that they can improve their own fitness for anaesthesia and surgery by a reduction in their consumption of cigarettes or tobacco with a view to giving up smoking for as long as possible before operation.

Unfortunately, there is a hard core of patients who totally ignore this advice and are reluctant to give up smoking for as little as 12 hours before operation. A few patients have indeed given up smoking but this number is offset by those who have actually been smoking more, 'because they are worried about coming into hospital'.

Therefore the plan by the Association of Anaesthetists of Great Britain and Ireland and the Health Education Council to produce a leaflet that explains the risks of smoking before surgery, is welcome; one hopes that it will have more success than my letter.

Barnet General Hospital,
Wellhouse Lane,
Barnet,
Herts. EN5 3DJ

I.E. Symons

Cellulitis as a complication of difficult tracheal intubation

The rare, but more serious complications of difficult tracheal intubation aided by a stylet include retropharyngeal abscess formation[1] after perforation of the posterior pharyngeal wall. We report a patient who developed almost total dysphagia associated with presternal cellulitis following a difficult tracheal intubation in which a stylet was used.

A 68-year-old female presented for tympanoplasty. She was in excellent health and had undergone a recent uneventful anaesthetic without tracheal intubation. The configuration of her teeth and mandible suggested that tracheal intubation might be difficult.

Anaesthesia was induced with thiopentone, and suxamethonium was given to provide relaxation for intubation. The upper surface only of the epiglottis could be seen on laryngoscopy. An attempt was made to introduce a stylet into the glottis by passing it blind posteriorly to the epiglottis after the standard means had been tried. On two occasions the stylet appeared to pass easily into the trachea but neither a latex armoured nor a plastic tracheal tube would pass beyond the epiglottis. By this time the suxamethonium had worn off and deep anaesthesia with spontaneous breathing was established with nitrous oxide and isoflurane in oxygen. A nasal tube was then passed blind without difficulty and the rest of the anaesthetic was uneventful. No further attempt was made to visualise the larynx at extubation.

The anticipated severe sore throat became even worse on the first postoperative day and, by the second day, had progressed to almost total dysphagia. On the third day an area of cellulitis about 10 cm in diameter appeared over the upper end of the sternum; the temperature was 38°C and there were signs of systemic toxicity. Indirect laryngoscopy gave no better view of the larynx than had been obtained at intubation; however, no pharyngeal damage was seen. A rapid improvement followed treatment with povidone iodine gargles and oral ampicillin, and the patient was discharged free of symptoms on the sixth day.

The use of a stylet to permit tracheal intubation where only the upper surface of the epiglottis can be seen, is a commonly used technique but is potentially dangerous. Alternative techniques are the use of a fibreoptic laryngoscope, which was not available on this occasion, the method of guided blind intubation following puncture of the cricothyroid membrane,[2] or use of the blind nasal route, as in this case.

Perforation of the pharyngeal wall with subsequent retropharyngeal abscess formation is, however, very rare considering the number of times stylets are so used. The cellulitis seen in our case was most probably caused by perforation of either the vallecula or one of the piriform fossae by the stylet; this would also explain the failure of intubation by this method.

We have not been able to find any previous reports of this complication of intubation. As would be expected, the infection, although highly alarming to both the patient and her doctors, yielded to simple treatment without the severe illness seen following retropharyngeal abscess formation.

Gloucestershire Royal Hospital,
Gloucester GL1 3NN

P.N. Young
J.M. Robinson

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Transillumination in fibreoptic intubation

Drs Davies and Hollway's communication about training in fibreoptic intubation (*Anaesthesia* 1986; **41:** 1265) prompts us to pass on a tip which we have found useful.

Our colleague, Dr T.H. Howells, at The Royal Free Hospital, has accumulated experience in blind orotracheal intubation with a Transilluminating Light Wand (Tube Stat; Concept Inc.) and, so far, has successfully intubated over 140 consecutive unselected cases with this instrument. The light wand has a bright light on its tip, which transilluminates through the tissues of the neck and guides the operator into the trachea.

We have found that study of the suitably shaded neck for transillumination from the tip of the fibrescope is often useful. Essentially, one is either deviated laterally (light seen) or not sufficiently far in or down the oesophagus (light not seen). The appearance of the light moving down the trachea is most characteristic.

We do not think there is much advantage in having the patient asleep since we have found, like others,[1,2] that the procedure is very well tolerated under topical anaesthesia and mild sedation. The great advantage of having the patient sufficiently awake to maintain his own airway, is that the operator is under no pressure to complete the procedure in a given time. There seems little point in giving up this advantage since topical anaesthesia takes the same time to apply whether the patient is asleep or awake.

The National Hospitals for Nervous Diseases, Maida Vale Hospital, London W9 1TL

J.E. WHITLOCK
I. CALDER

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Correct placement of bronchial tubes

In reply to Dr Duncan's letter (*Anaesthesia* 1986; **41:** 1270) about correct placement of double lumen tubes, we do indeed have a smaller diameter bronchoscope. The Olympus LF-I has an external diameter of 3.8 mm and is designed specifically to aid in tracheal intubation of difficult patients and verification of placement of double lumen bronchial tubes.[1]

This instrument will pass readily down either lumen of standard size PVC tubes (e.g. 35, 37, 39 or 41 Fr Bronchocath, 5.0, 5.5 or 6.0 mm Portex tracheal tubes), the larger sized red-rubber tubes (e.g. 37, 39 or 41 Fr Carlen's (left) or White's (right)) and the medium and large Robertshaws. It does not pass down the newly introduced 28 Fr Bronchocath, nor the 35 Fr Carlen's/White's and small Robertshaw, although there are paediatric fibrescopes with external diameters as small as 2.7 mm (Olympus PF-27M).[2]

It is possible to view the origin of the right upper lobe bronchus via the aperture in the bronchial cuff of a right-sided bronchocath but, as we stated in our letter, we much prefer to use left-sided tubes whenever possible since they are so much easier to place.[3]

This unit provides anaesthesia for over 500 major thoracic surgical procedures annually and we use fibreoptic bronchoscopy routinely accurately to confirm the placement of double lumen tubes[4,5] employing documented techniques.[6]

Wentworth Hospital, Private Bag Jacobs 4016, Durban, South Africa

R.G. MACGILLIVRAY
D.A. ROCKE
A.E. MAHOMEDY

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Peri-operative fluids

The paper by Drs Twigley and Hillman (*Anaesthesia* 1985; **40:** 860–71) on peri-operative fluid administration was very interesting and forms an excellent basis upon which to consider this important subject. However, I would suggest that the case for colloids, and against crystalloids, in routine surgery not associated with significant blood loss, is not yet proven. Many aspects have been studied but there is a confusing array of evidence to support each side of the case.

The arguments against crystalloids centre around

the obligatory retention of sodium and water in the peri-operative period, an increase in pulmonary interstitial fluid with consequent impairment of gas exchange, and a reduced renal protective effect. In addition, peri-operative monitoring of the cardiovascular system reveals changes in the vascular compartment which can be more readily altered by colloids because they tend to remain in the vascular compartment. However, these aspects have all been disputed.

Some recent research has suggested that sodium and water retention (far in excess of net blood loss) may be a normal physiological response to a decrease in extracellular fluid volume[1] and can be reduced or prevented by infusion of crystalloids.[2] The extracellular volume is notoriously difficult to measure and whether replacement of this deficit is beneficial or harmful, would be even more difficult to prove.

The pulmonary effects have also been debated. Plasma colloid osmotic pressure does decrease with large volumes of crystalloid but it has been shown that extravascular lung water does not depend on plasma colloid osmotic pressure[3] and does not necessarily increase with infusion of large volumes of crystalloid.[3,4] The reasons advanced for this are that pulmonary interstitial fluid has a high concentration of protein, which thus minimises transcapillary osmotic pressure changes, and that pulmonary lymphatic flow can increase dramatically to remove excess fluid. Changes in lymph flow and hydrostatic pressure may be relatively more important in the development of interstitial oedema than colloid osmotic pressure.

The relationship between anaesthesia, surgery and renal function is complex and the relative protective effects of crystalloids or colloids have not been proven. It is easier to measure the effects of anaesthesia, surgery and intravenous fluids on the intravascular compartment but the changes in the interstitial and intracellular compartments deserve our attention. The definitive answer awaits the further elucidation of lung fluid balance mechanisms and the interstitial fluid volume changes associated with surgery. In view of the occasional hazards of colloid administration and the conflicting evidence available, it seems reasonable for the clinician to reserve judgement in the meantime.

Stobhill Hospital,
Glasgow

A.J. Bennett

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A reply

Thank you for the opportunity to reply to Dr Bennett's letter. He raises many points and most of these are covered in our original article; I do not agree that there is controversy about whether colloids correct hypovolaemia more efficiently than crystalloids. Even the most inefficient colloid remains in the intravascular compartment longer than crystalloids.

Sodium and water retention has been known for many years to be a normal physiological response to a decrease in extracellular fluid volume. However, the amount of sodium and water retention cannot be compared to the amount of blood lost. Blood is intravascular fluid and about two-thirds of salt and water is interstitial fluid. Just as administration of excessive amounts of crystalloid is an inefficient way to replace intravascular losses, the body's own protective mechanism of salt and water retention is an inefficient way to maintain circulating volume. One of the articles quoted[1] from Dr Bennett's letter supposedly suggests that a decrease in extracellular fluid volume can be reduced or prevented by 'infusing' crystalloids. In fact, it shows that crystalloids decrease the colloid osmotic pressure (COP) and expand the interstitial space. The authors[1] then point out the dangers of this and suggest that COP is maintained in the postoperative period.

There is confusion about the optimal extracellular volume in the peri-operative period. In my opinion, it is because the wrong question is being addressed. The extracellular volume consists of two fluid spaces with different composition and function, the intravascular space and the interstitial space. No-one would argue about maintenance of the intravascular space. However, the interstitial space is protected largely by salt and water retention, and excessive interstitial volume can cause interstitial and pulmonary oedema.

Dr Bennett is quite correct to point out that in normal patients, peripheral oedema occurs far more readily than pulmonary oedema. However, in the seriously ill, pulmonary oedema occurs far more readily with crystalloid therapy than with colloids. The peripheral oedema that occurs when crystalloid fluids are used in the peri-operative period, results because they expand mainly the interstitial space, not the intravascular space. There is now strong evidence that peripheral oedema can cause multiple organ dysfunction and delayed wound healing (see our article).

Finally, the use of the term 'protective effect' when referring to crystalloids and colloids, is woolly and misleading. Maintenance of the intravascular volume is essential for tissue perfusion, whereas even relatively minor interstitial space overexpansion causes oedema which results in decreased tissue perfusion. Neither

crystalloids nor colloids are efficient at replacing the two spaces which comprise the extracellular fluid volume and neither, therefore, offers 'protection' to the extracellular fluid space. Colloid solutions are more efficient for the replacement of intravascular volume, and crystalloid solutions are more efficient for the replacement of interstitial fluid volume.

The Liverpool Hospital,
Liverpool,
NSW 2170,
Australia

K.M. HILLMAN

Reference

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Editor's note: this correspondence is now closed.

Error in labelling

In our hospital, disposable polyvinyl chloride bronchial tubes have recently been introduced as an alternative to red-rubber double lumen tubes on the basis of longer shelf-life, cost effectiveness and ease of bronchial placement.

A manufacturing error of labelling was recently found on a 35-FG left disposable bronchial tube (Mallinckrodt Critical Care Bronchocath). Both pilot balloons were identically labelled 'bronchial'.

We wish to draw attention to this possible hazard which could be overlooked during routine pre-operative cuff checks, unless specific reference is made to the labelling.

Bradford Royal Infirmary,
Bradford 9

P. BICKFORD-SMITH
C.S. EVANS

A reply

This appears to be an isolated incident of an error which occurred during assembly of the product and which was not identified during quality control checks. Unfortunately Drs Bickford-Smith and Evans were unable to supply us with the identification lot number of the product involved.

In common with all manufacturers who operate under the DHSS Guide to Good Manufacturing Practices Registration Scheme, we maintain full records of the manufacture of every product throughout every stage of manufacture and this history can be traced through the lot number. Lot numbers are printed on every packet and box and we would like to stress to all readers the importance of this information when a problem with any product is discovered.

Mallinckrodt,
11 North Portway Close,
Northampton NN3 4RQ

D.G.L. WOOD

Low dose infusion of dopamine

The article by Dr Polson *et al.* (*Anaesthesia* 1987; **42:** 7–14) about the prophylactic use of low dose dopamine in patients undergoing orthotopic liver grafting was interesting since we reported some measurements from the Royal Liverpool Hospital on the effect of low dose dopamine (2 μg/kg/minute) upon renal function during aortic cross clamping.

An investigation [1] was prompted by the finding that a profound alteration in renal haemodynamics occurred during infrarenal cross clamping, characterised by a 75% increase in renal vascular resistance and a 38% decrease in renal blood flow which persisted for about one hour after the release of aortic clamping, despite infusion of mannitol, maintenance of cardiac output and renal perfusion pressure.[2] Our results were comparable to Dr Polson's. There were significant increases of creatinine clearance ($p < 0.05$) and urine flow ($p < 0.05$) when dopamine was given.

My recommended practice now is to administer dopamine infusion (2 μg/kg/minute) after induction of anaesthesia and throughout the operative period. Neither osmotic nor loop diuretics are employed.

Haltan General Hospital,
Runcorn,
Cheshire WA7 2DA

M.G.D. SALEM

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AIDS and anaesthesia

Drs Lee and Soni's article on AIDS and anaesthesia (*Anaesthesia* 1986; **41:** 1011–16) was interesting. In this country, the AIDS epidemic is more prevalent than in England and so, even in the operating room in this institution, every patient is treated as HTLV III antibody positive. Gloves are worn by anaesthetists for protection when intravenous or arterial lines are established; they are also worn for all intubations and for aspiration of secretions even though the infectivity of secretions is in doubt.

Patients are also given options to protect themselves. All elective patients scheduled to undergo procedures that might require blood transfusion, are asked to donate autologous blood a few weeks before and are then put on iron supplements. In other cases, the anaesthetist is also trained to be hesitant in giving blood transfusions. Most patients are given infusions of crystalloids and colloids as long as the cardiovascular system is stable. It is only when the haematocrit (Hct) falls to 30% or less in the younger patient (as worked out from the formula, allowable blood loss = total blood volume/starting Hct × 30), does the anaesthetist start to consider a blood transfusion.

If all these factors are taken into account, perhaps, anaesthetists can hope to reduce the chance of infection by this virus to themselves and to their patients.

Johns Hopkins Hospital,
Baltimore, MD 21205,
USA

L.M. VELLA

A traumatic nasotracheal intubation

Further to the correspondence on this subject (*Anaesthesia* 1986; **41:** 1057–8), another way to reduce trauma is simply to immerse the first few inches of the plastic tracheal tube in hot water for a few minutes just before it is inserted. This temporarily softens the plastic and if the tip of the tube is also well lubricated it usually passes easily through the nose (of course, hot water does not soften a rubber tube).

1393 Oak Avenue,
Los Altos,
CA 94022, USA

D.V. THOMAS

Anaesthesia, 1987, Volume 42, pages 574–581

Anaesthetic literature

This section of *Anaesthetic literature* contains references taken from *Current Contents—Life Sciences* for December 1986. The Journals which may be consulted when *Anaesthetic literature* is compiled are those listed in *Current Contents—Life Sciences*, published by the Institute of Scientific Information, Philadelphia, Pennsylvania, USA.

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Other drugs

Famotidine: an appraisal of its mode of action and

The collator of this section is Dr L. Kaufman, MD, FFARCS, Anaesthetic Office, The Rayne Institute, University College, University Street, London WC1E 6JJ. Dr Kaufman is prepared to provide on request, and at a modest charge, a new additional service to our readers. References from January 1984 have been entered on data base. The data are held on Dbase II, and are available on disk, together with a program providing search facilities. Enquiries direct to Dr Kaufman at the above address please.

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Anaesthesia, 1987, Volume 42, page 582

Erratum

Anaesthesia, 1986, Volume 41, pages 861–865

Management of a glomus jugulare tumour with carotid artery involvement

B. M. BRAUDE, R. HOCKMAN, W. A. McINTOSH AND D. HAGEN

In the third paragraph of the second column on p. 862, the second dosage of thiopentone was given incorrectly as 33 g. The correct version should read:

During the hour prior to intracranial carotid clamping, an infusion of thiopentone 1 g was given; in the 2.5 hours following internal carotid artery ligation, a further 3 g thiopentone was infused. In addition, the patient received 300 mg hydrocortisone intravenously. Mannitol 20 g was administered to improve operative conditions for neurosurgery.

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Corporate author

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. *Scandinavian Journal of Clinical Laboratory Investigation* 1976; **36:** 119–25.

Anonymous. Epidemiology for primary health care. *International Journal of Epidemiology* 1976; **5:** 224–5.

BOOKS AND OTHER MONOGRAPHS

Personal author(s)

OSLER AG. *Complement: mechanisms and functions*. New York: Prentice-Hall, 1976.

Corporate authors

American Medical Association Department of Drugs. AMA drug evaluations, 3rd edn. New York: Publishing Sciences Group, 1977.

Editor, compiler, chairman as author

RHODES AJ, VAN ROOVEN CE, *comps. Textbook of virology: for students and practitioners of medicine and other health sciences*, 5th edn. Baltimore: The Williams & Wilkins Co., 1968.

Chapter in book

WEINSTEIN L, SWARTZ MN. Pathogenic properties of invading micro-organisms. In: SODEMAN WA Jr, SODEMAN WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W.B. Saunders, 1974: 457–72.

Agency publication

National Center for Health Statistics. Acute conditions: incidence and associated disability, United States, July 1968—June 1969. Rockville, MD: National Center for Health Statistics, 1972. (*Vital and health statistics, Series* **10:** Data from the National Health Survey, No. 69) [DHEW publication No. (HSM) 72–1036].

OTHER ARTICLES

Newspaper article

SHAFFER RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help to cure alcoholism and insomnia, explain mental illness. How the messengers work. *Wall Street Journal* 1977 Aug 12: 1(col 1), 10(col 1).

Magazine article

ROUECHE B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971 Sept 4: 66–81.

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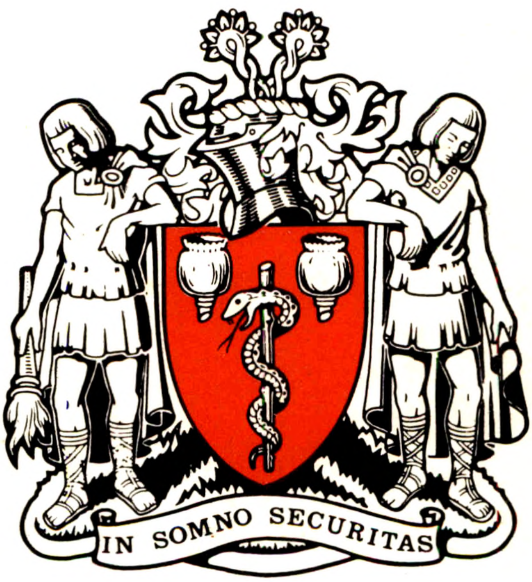

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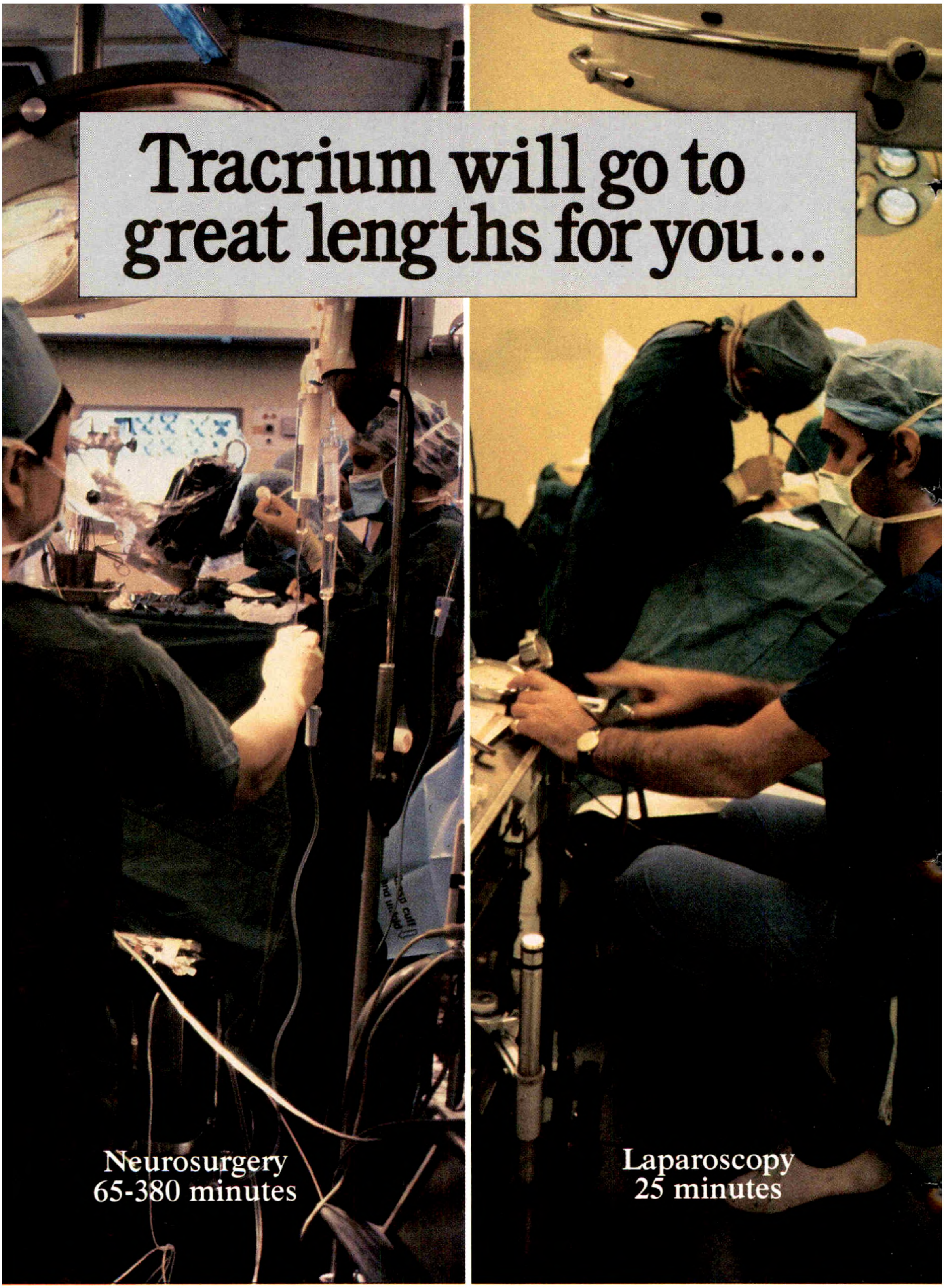

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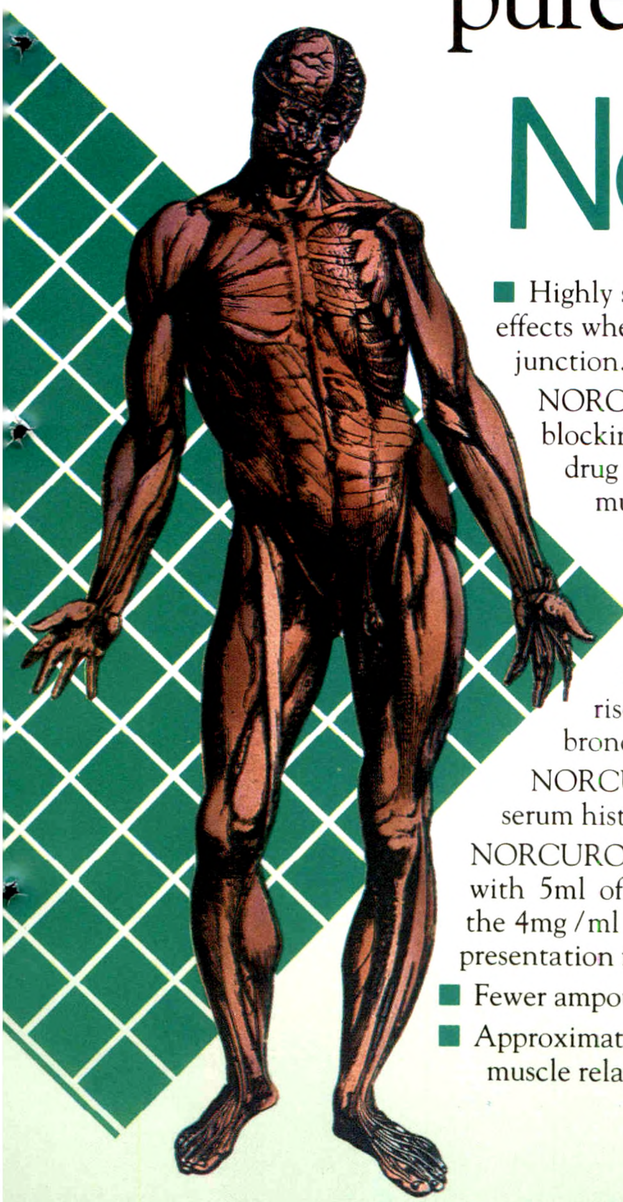

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Anaesthesia, 1987, Volume 42, pages 583–585

Editorial

Clinical investigations—why we must keep control

Few things can be more frustrating for the keen young researcher, or the senior registrar intent on embellishing his curriculum vitae, than to have a manuscript that represents many months of work on a clinical research project rejected by the editor of a journal on the grounds that the investigation was inadequately controlled.

What degree of control is necessary? Controlled clinical trials are undertaken on samples of a population and their design must ensure, as far as possible, that the *only* difference between sample groups is the form of treatment which is being investigated. The existence of a control group *per se* is insufficient to ensure that the findings are accurate and unbiased.

Clinical trials are fraught with problems.[1] If large numbers of patients are required, or the condition being investigated occurs uncommonly, it may be tempting to study the new method of treatment prospectively in a group of patients and to compare the outcome with results acquired retrospectively from a control group of apparently similar patients. For example, reinfarction rates following anaesthesia were studied prospectively in patients who received intensive monitoring and found to be significantly lower than in patients who had been treated in the same institution, but with 'minimal invasive monitoring', during a 3-year period preceding the start of the investigation.[2] The recommendation of the authors that patients at risk should be monitored in an intensive care unit for up to 96 hours after surgery, appeared to be amply justified on initial reading of the paper but was rejected in an accompanying editorial[3] which drew attention to potential inaccuracies inherent in a study of this type. Indeed, it has been established that the use of historical controls results in bias in favour of the new treatment[4] for reasons which include differences in patient selection, improvements in general patient care and acquired experience of medical and nursing staff.

Prospective comparisons may also be inaccurate. In almost all prospective clinical trials in anaesthesia, patients are allocated by some random selection procedure into control and treatment groups. However, when the sample size is small, randomisation may not produce samples from the same population. Age and gender are known to influence the effects of a number of anaesthetic drugs;[5,6] baseline values of a variable under investigation may be different, which makes interpretation of subsequent changes very difficult; or there may be an uneven distribution of patients taking medication for unrelated conditions, but which may influence the effects of the treatment under investigation. Consequently, it may be advisable in some instances to use a stratified sampling technique[7] in order to ensure even matching of characteristics between study groups.

Sample size is important, but frequently selected for reasons of convenience rather than science. Small samples may result in rapid completion of a study but increase the risk of Type II (false negative) errors. Of 71 negative randomised controlled trials re-examined by a group of statisticians,[8] 80% could have demonstrated a difference between groups if the sample size had been larger.

It is important to establish that the comparison being made is valid. Should a placebo group be included? The placebo effect in studies of analgesic or sedative drugs is well recognised but often ignored. There are, of course, many instances when a placebo effect is unlikely to occur, and when a direct comparison between two different drugs or techniques is appropriate. However, the results of a comparative study may be misinterpreted if different methods of treatment are not equivalent in, for example, their potency. A recent study[9] that compared total intravenous and inhalational anaesthesia concluded that the risks of intra-operative movements, dreaming and awareness were higher if inhalational anaesthesia was used. However, calculations based on the data presented reveal that patients in one group received 1 MIR[10] (minimum infusion rate, the equivalent for intravenous anaesthetic agents of MAC for inhaled anaesthetics) of etomidate but in the other group, only 0.6 MAC of inhalational agent was administered; thus, another interpretation of the results is that patients show more signs of awakening if they are inadequately anaesthetised!

The independence of the observer is another crucial factor in controlling variables in a study, especially when subjective measurements are made, for example the quality of intubating conditions, degree of pain, sedation or anxiolysis. Bias, even if subconscious, is likely unless the observer is blinded to the treatment allocated to the patient under investigation. Variability is introduced if more than one observer is used. Common examples are the use of recovery room or ward staff to collect data and, even more unreliable, assessment of analgesic requirements in the postoperative period based on administration by ward nurses from an 'as required' prescription.

Statistical analysis is another source of inaccuracy in the presentation of results from clinical trials. The use of inappropriate tests may result in Type I (false positive) errors. For example, pain scores are often analysed as interval rather than ordinal data; is 2 cm of pain on a linear analogue scale twice as bad as 1 cm of pain? The finding of statistical significance appears to be the sole objective of many investigators, irrespective of the clinical significance of the results. This approach has been criticised strongly in recent authoritative articles[11,12] and, in future, it is likely that journal editors will encourage the presentation of confidence intervals rather than standard errors or significance limits.

Most of the principles described above are well known to all anaesthetists, even at a junior level. It is, therefore, disappointing to find in surveying the British anaesthetic literature in 1986 that one or more of these principles was not adhered to in 21% of 'controlled' clinical trials published as Clinical Investigations in the *British Journal of Anaesthesia* or as Main Articles in *Anaesthesia*. In addition, many manuscripts are rejected by the editors of these journals because inadequate control was incorporated in the design or execution of the study.

Relatively few earth-shattering discoveries are likely in anaesthetic research; it is probable that most of them have been made already. The majority of contemporary research in the United Kingdom consists of clinical drug trials or fine tuning of established techniques.[13] It is, therefore, all the more important that we achieve accuracy in the presentation and interpretation of results. Clinical trials which produce inaccurate or biased findings are bad for the specialty and potentially hazardous for the patient.

University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW

A.R. AITKENHEAD
Assistant Editor

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Editorial notices

Submission of manuscripts

Manuscripts must be submitted in accordance with the internationally recognised *Uniform requirements for manuscripts submitted to biomedical journals* (*British Medical Journal* 1979; **1**: 532–5). Details will be found in the Notice to Contributors to *Anaesthesia* at the end of this issue.

Anaesthesia News

Copy for *Anaesthesia News* should be sent to the Editor as and when it becomes available. It is hoped that publication will occur within 3 months of receipt.

Anaesthesia, 1987, Volume 42, pages 586–590

Pregnanolone emulsion

A new steroid preparation for intravenous anaesthesia: an experimental study in mice

S. HØGSKILDE, J. W. NIELSEN, P. CARL AND M. B. SØRENSEN

Summary

The anaesthetic activity of pregnanolone (a metabolite of progesterone) in emulsion formulation administered intravenously to male mice was compared with that of Althesin. The loss of righting reflex for 15 seconds was used to estimate the anaesthetic effect. The mean anaesthetic dose (AD_{50}) for the pregnanolone emulsion was 5.25 mg/kg and for Althesin, 2.8 mg/kg. The mean lethal dose (LD_{50}) was 44 mg/kg for pregnanolone and 54 mg/kg for Althesin. The sleeping time after pregnanolone was 2.5–3.5 times longer than after Althesin in dosages above 7.5 mg/kg. No signs of pain or local reaction from injection were observed for either of the drugs. The onset of action was fast for both drugs, with only minor signs of excitation, and recovery was rapid and without excitation. The results indicate that the anaesthetic properties of pregnanolone emulsion are very similar to those of Althesin. Further studies will show whether it can fill the major vacuum left in anaesthetic practice after the withdrawal of Althesin.

Key words

Anaesthetics, intravenous; Althesin, pregnanolone.

The anaesthetic and anticonvulsive properties of certain steroids were originally demonstrated 45 years ago by Selye.[1,2] Since then, comprehensive work has been undertaken to employ these properties for clinical use. Two main problems had to be solved. Firstly, the other hormonal activities had to be separated from anaesthetic and anticonvulsive actions. Secondly, these highly lipophilic substances had to be prepared in a pharmaceutically acceptable formulation for intravenous use.

In the past, three steroidal agents have fulfilled these criteria and have been used clinically as anaesthetics. Hydroxydione was introduced in 1955 by Laubach and co-workers.[3] It had a high therapeutic index but was withdrawn because of several disadvantages, such as a slow induction time and high incidence of thrombophlebitis. Ten years later, it was found that the anaesthetically active steroid, 3-α-hydroxy-5-α-pregnane-11,20-dione, could be solubilised in saline by addition of its less active 21-acetoxy derivative and the polyoxyethylated castor oil derivate, Cremophor EL.[4] This preparation was introduced under the trade name Althesin and appeared to have many properties of an ideal intravenous anaesthetic.[5,6] Serious, and in some cases fatal, allergic reactions due to the Cremophor EL caused this otherwise excellent drug to be withdrawn from clinical use.

S. Høgskilde, MD, J.W. Nielsen, MD, P. Carl, MD, M.B. Sørensen, MD, PhD, Chief Anaesthetist, Department of Anaesthesiology and Intensive Care, The Municipal Hospital of Copenhagen, DK 1399 Copenhagen K, Denmark.

This work was performed at the Department of Anaesthesiology and Intensive Care and the Department of Pathology, The Municipal Hospital of Copenhagen, Denmark.

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Clinical tests were begun in 1979 with the water-soluble steroid, minaxolone.[7,8] Excitatory effects during induction and a slow recovery were, however, major drawbacks.[9] The drug was withdrawn from clinical trials in 1980 following questionable toxicological findings in rats.[9] Further clinical evaluation has not been resumed, even though the findings were refuted in this respect.[10]

In 1957 Figdor and co-workers[11] reported a series of structurally related pregnanes which had anaesthetic activity when administered intravenously to mice in a finely ground, aqueous suspension. The group of compounds did not demonstrate notable endocrine action. The most potent agent found was pregnanolone (5-β-pregnan-3-α-ol-20-one),[11] a metabolite of progesterone. This naturally occurring[12] anaesthetic agent has now been prepared in a stable emulsion which may prove suitable for clinical use. The present study in mice compares the anaesthetic effect of this new preparation, to that of Althesin.

Methods

Male NMRI mice weighing 26–36 g and aged 8–12 weeks were used for the investigation. All injections were given via a tail vein with a duration of delivery of 15–30 seconds. The mice were then placed in separate boxes to avoid external stimuli. The criterion used to estimate the anaesthetic effect was loss of the righting reflex for at least 15 seconds. As long as the mouse is conscious, it will not accept being placed on its side or back but will return to its feet immediately. All animals were allowed free access to food and water except during the injections. The mice were observed for 24 hours after which they were sacrificed.

Pregnanolone was dissolved in soya bean oil and emulsified a similar way as Intralipid and Diazemuls. The pregnanolone emulsion consisted of pregnanolone 4 mg, soya bean oil 200 mg, acetyl triglycerides 70 mg, egg yolk phosphatides 18 mg, glycerol 17 mg and distilled water to 1 ml.

The emulsion is isotonic and has a pH of *ca.* 7.5. The mean particle size of the emulsion is in the region of 0.2–0.5 μm, and less than 3% of particles are larger than 1.0 μm. The pregnanolone emulsion was diluted with Intralipid 20% at doses below 45 and 50 mg/kg to allow an accurate injection volume of 10 ml/kg (0.3 ml/mouse).

Althesin contains 12 mg of steroid/ml. It is an aqueous suspension that contains alphaxolone 9 mg/ml, alphadolone 3 mg/ml and Cremophor EL 200 mg/ml. Althesin was diluted with 0.9% NaCl in order to obtain a similar injection volume of 10 ml/kg.

To determine the mean anaesthetic dose (AD_{50}) and the mean lethal dose (LD_{50}), groups of eight mice were tested at different dosage levels. The dosage limits where all or none of the mice in a batch were asleep and the dosage limits where all or none of the mice in a batch died, plus at least three points between each of these limits, were established. The LD_{50} and AD_{50} were estimated for the pregnanolone emulsion, Althesin, Intralipid and 0.9% NaCl by the Licthfield and Wilcoxon method.[13]

The results were analysed statistically using the Mann–Whitney unpaired rank sum test. Significance was assigned at a level of $p < 0.05$. Duration of sleep, defined as the total time of loss of the righting reflex, was recorded for each animal and plotted as a semilogarithmic dose–response curve.

Results

The AD_{50} for pregnanolone emulsion was found to be 5.25 mg/kg and the corresponding value for Althesin was 2.8 mg/kg (Table 1). The difference in the AD_{50} values was not statistically significant ($p > 0.1$). The LD_{50} for pregnanolone emulsion was 44 mg/kg and for Althesin, 54 mg/kg (Table 1). This difference also proved not to be significant ($p > 0.1$). Death occurred within 2 minutes after administration of lethal doses of Althesin, whereas after lethal doses of pregnanolone emulsion the mice died within a period of 4–180 minutes with a mean time of death of 43 minutes. The therapeutic index (LD_{50}/AD_{50}) was calculated as 8.4 for pregnanolone emulsion and 19.3 for Althesin (Table 1).

The semilogarithmic dose–response curves for pregnanolone emulsion and Althesin, as well as the survival ratio at each dose, are illustrated in Fig. 1. The sleeping time after pregnanolone emulsion in doses above 7.5 mg/kg, was 2.5–3.5 times longer compared to that after Althesin at the same dose level (mg/kg).

Table 1. Mean anaesthetic dose (AD_{50}), mean lethal dose (LD_{50}) and therapeutic index (TI) of intravenously administered pregnanolone emulsion and Althesin in male mice.

Substance	AD_{50} (mg/kg)	LD_{50} (mg/kg)	TI (LD_{50}/AD_{50})
Pregnanolone emulsion	5.25	44.0	8.4
95% Confidence interval	4.95–5.57	38.7–50.0	
Slope of regression line	1.09	1.30	
Althesin	2.80	54.0	19.3
95% Confidence interval	2.04–3.84	42.86–68.04	
Slope of regression line	1.57	1.59	

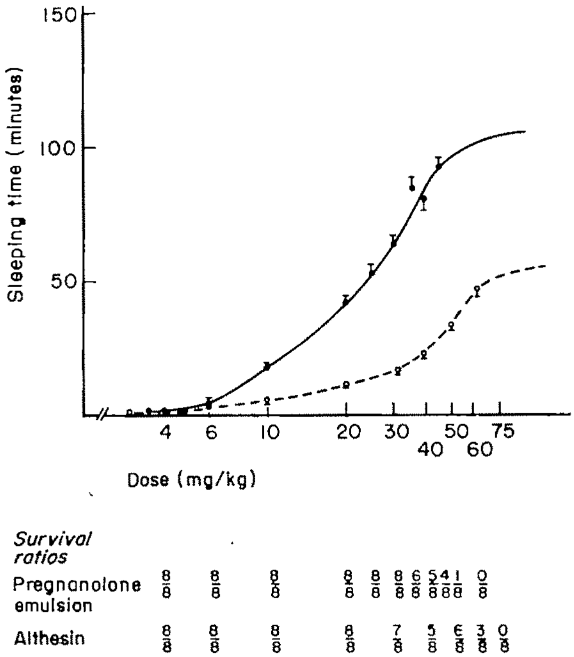

Fig. 1. Logarithmic dose–response curves after intravenous injections of pregnanolone emulsion and Althesin in groups of eight male mice. *Survival ratio*: the numerator represents the number of surviving animals. ——, Pregnanolone emulsion; – – – –, Althesin.

The onset of action of the two drugs was found to be comparable. The mice fell asleep within one minute after injection. In the dosage range below and just above AD_{50}, about 50% of the mice showed minor signs of excitation during induction. There were no differences between the drugs and, above $2 \times AD_{50}$, excitation was rare. No signs of pain on injection or local reaction at the injection site were observed for either of the drugs.

Recovery from anaesthesia was uneventful and only a few mice showed minor signs of excitation. After a period with signs of ataxia all animals behaved quite normally within 5–25 minutes after they awoke, and several of the animals ate shortly after they regained the righting reflex.

Injection of Intralipid or 0.9% NaCl alone had no anaesthetic effect and both were tolerated in large amounts; the LD_{50} for Intralipid was 163 ml/kg (135–197 ml/kg) and for 0.9% NaCl, 232 ml/kg (193–278 ml/kg).

Discussion

The results presented indicate that the anaesthetic properties of a pregnanolone emulsion are similar to those of Althesin. It produces immediate induction of anaesthesia of short duration. Excitation during induction is not pronounced and the recovery is rapid and uncomplicated. The therapeutic index is favourable and intravenous injection is unproblematical.

The AD_{50} value of 5.25 mg/kg for pregnanolone emulsion obtained in this study is a little lower than that found by Figdor *et al.*[11] (6 mg/kg), but higher than the values published by Gyermek[14] (2.3 mg/kg) and Banks and Peace[15] (2.0 mg/kg). In the study by Figdor *et al.*[11] the steroid was administered as a fine aqueous suspension while in the last two studies, propylene glycol, which is known to possess central nevous system depressant action of its own,[16–18] was used to dissolve the steroid. These differences in preparation, as well as differences in the definition of effect, injection rates and concentrations used, may explain the differing results. A further factor that could also explain some of the disparity, is a possible slow release effect from the emulsion form compared to the solutions used in the other investigations.

The LD_{50} value of 44 mg/kg for pregnanolone found in this study is lower than those published earlier by Gyermek[14] (66 mg/kg) and Figdor *et al.*[11] (89 mg/kg).

For Althesin an LD_{50} of 54 mg/kg and an AD_{50} of 2.8 mg/kg were obtained. Child *et al.*[19] and Davis and Pearce[20] found a similar LD_{50} but an AD_{50} value of only 1.8 mg/kg. Al-Khawashki *et al.*[21] found an LD_{50} of 47 mg/kg and an AD_{50} of 2.1 mg/kg. Again, differing criteria used to estimate AD_{50} may explain the different values found. The total times of loss of the righting reflex found by Child *et al.*[19] and by Davis and Pearce[20] after various dosages, are very close to the sleeping times estimated in this study.

The therapeutic index for the pregnanolone emulsion was less than half the index found for Althesin. However, the mean sleeping time after pregnanolone emulsion was longer than after Althesin in doses above AD_{50}. If this lower effect of Althesin is taken into consideration and the estimate of the AD_{50} values is done at a time limit higher than 15 seconds, the proportions between the therapeutic indices would diminish and eventually shift.

In our opinion it appears from this study in mice that pregnanolone emulsion has an excellent anaesthetic effect. Further studies will show whether it can fill the major vacuum left in anaesthetic practice after the withdrawal of Althesin.

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Premedication for day case surgery

A study of oral midazolam

D. RAYBOULD AND E. G. BRADSHAW

Summary

A double-blind, between-patient trial was used to assess midazolam 7.5 and 15 mg as oral premedication for day case surgery. Midazolam 7.5 mg did not produce significant anxiolysis or sedation in comparison to placebo as measured by patient self-assessment linear analogue scales and observer scores. Midazolam 15 mg caused significant anxiolysis and sedation pre-operatively but also at 2 hours following awakening. Psychomotor performance assessed by digital-symbol substitution tests was significantly impaired by midazolam, in both doses, throughout the period of investigation. Midazolam 15 mg orally provides good premedication but the prolonged effects make it unsuitable for short-stay patients.

Key words

Hypnotics, benzodiazepines; midazolam.
Premedication.

The majority of patients entering hospital for surgery are anxious or afraid [1,2] and benefit from pre-operative medication. Day case surgery demands a rapid recovery from anaesthesia and return to street fitness [3] and, consequently, pre-operative medications which may be long-acting, are often withheld.

Midazolam is a potent imidazobenzodiazepine which possesses typical benzodiazepine properties, namely, hypnotic and anxiolytic activity. It is rapidly absorbed and short-acting, having an elimination half-life [4] of about 2 hours. This trial was designed to test the suitability of midazolam, administered orally, as a premedicant for day case surgery.

Methods

A double-blind, between-patient trial was designed to include 60 patients who presented for day case surgery. All patients were between 16 and 65 years of age, ASA grade 1 or 2 and were not receiving any concurrent psychotropic medication. The operations were minor orthopaedic, gynaecological and general surgical procedures. All patients were admitted to either a day surgical ward or a general surgical ward and were included in regular operating sessions. The protocol for the study was approved by the local hospital ethical committee.

After informed consent had been obtained, they were allocated at random to one of three groups. Group A received placebo, group B received midazolam 7.5 mg and group C received midazolam 15 mg. All patients received a gelatin capsule with up to 20 ml of water, 1 hour before the estimated time of the operation. They were asked to perform the following tests immediately after the ingestion of the capsule (zero time) and after careful explanation.

D. Raybould, MB, ChB, FFARCS, Research Fellow, Department of Anesthesiology, UCLA School of Medicine, Center for Health Sciences, Los Angeles, CA 90024, USA, E.G. Bradshaw, MD, FFARCS, Consultant, Ealing Hospital, Uxbridge Road, Southall, Middlesex.

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Anxiety and sedation. The patients were asked to score their anxiety and level of sedation on a 10-cm linear analogue scale and the score from zero anxiety or zero sedation was recorded. In addition, the observer scored the patients' anxiety on a three-point scale: 1, not anxious; 2, anxious; 3, extremely anxious. Sedation was assessed by the observer on a five-point scale: 0, wide awake; 1, 'glassy eyed'; 2, sleepy but wakes on observer approaching the bed; 3, sleepy but wakes on being spoken to; 4, sleepy but wakes on being shaken; 5, unrousable. The observer was trained, was the same throughout and was unaware of the medication given.

Psychomotor performance. A standardised digital-symbol substitution test was performed to assess psychomotor performance: the number of correct substitutions in 60 seconds was taken as a control value. Improvement or impairment of the score was recorded subsequently.

Memory. Short-term memory was assessed by showing the patients a particular symbol at the start of the test period and later testing their recall of it.

All these tests were repeated at 30 and 60 minutes after ingestion of the capsule. Changes in the analogue scores from the zero time score were used in analysis. A different code of symbols was used on each digital-symbol substitution test to nullify the effect of medium-term memory.

The time of induction of anaesthesia was noted. General anaesthesia was induced with thiopentone and maintained with nitrous oxide, oxygen and halothane given via a Bain co-axial system and supplemented with fentanyl 1 μg/kg. The duration of the operation was recorded. After the procedure, the time to correct response, that is, to give name and address correctly, was recorded by recovery room staff. One and 2 hours after the latter time the tests of sedation, psychomotor performance and short-term memory were repeated. Any untoward events which might have been attributed to the premedication were recorded and, on leaving hospital, the patient was asked whether the capsule had been helpful to him/her and whether he/she would want to take the drug again. Arterial blood pressure, respiratory rate and pulse rate were recorded on admission to hospital, on admission to the anaesthetic room and at the time to correct response.

Results were analysed using Student's *t*-test and the Mann–Whitney U test.

Results

The three groups of patients were matched with respect to age, sex and weight (Table 1). Several patients had to be withdrawn from the study because of problems in the timing of the operation or because more major surgery was indicated. Data from 53 patients were available for analysis.

The time interval between administration of premedication and the induction of anaesthesia, the duration of the operation and the time to correct response were similar in all three groups (Table 2). The group that received midazolam 15 mg displayed longer recovery times but these did not achieve statistical significance.

Anxiety. The corrected linear analogue scale scores and observer assessments of anxiety are shown in Table 3. Midazolam 15 mg produced a significant degree of anxiolysis compared with placebo at 60 minutes ($p < 0.01$).

Table 1. Demographic data of patients included in the study.

		Age, years		Weight, kg	
Group	Male:female	Mean (SEM)	Range	Mean (SEM)	Range
Placebo (n = 16)	6:10	29 (2.4)	19–50	66 (3.0)	52–92
Midazolam 7.5 mg (n = 19)	7:12	42 (3.5)	20–64	74 (3.3)	55–100
Midazolam 15 mg (n = 18)	10:8	36 (3.6)	18–64	75 (4)	54–95

Table 2. Time intervals measured in the study.

	Mean (SEM) time interval, minutes		
Group	Premedication to induction	Duration of operation	Time to correct response
Placebo	95.9 (5.0)	34.9 (3.6)	6.9 (1.1)
Midazolam 7.5 mg	79.2 (4.8)	38.0 (2.9)	6.0 (0.8)
Midazolam 15 mg	102.2 (7.1)	47.0 (6.1)	10.5 (2.8)

Table 3. Assessment of anxiolysis.

Group	Mean (SEM) corrected linear analogue scores		Mean (SEM) observer scores		
	Zero time to 30 minutes	Zero time to 60 minutes	Zero time	After 30 minutes	After 60 minutes
Placebo	−0.4 (0.4)	+0.2 (0.6)	1.4 (0.4)	1.3 (0.4)	1.4 (0.1)
Midazolam 7.5 mg	−0.4 (0.4)	−0.6 (0.5)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)
Midazolam 15 mg	−1.1 (0.5)	−1.3 (0.3)*	1.4 (0.1)	1.3 (0.1)	1.1 (0.1)*

* $p < 0.01$.

Table 4. Assessment of sedation.

Group	Mean (SEM) corrected linear analogue scores				Mean (SEM) observer scores			
	After 30 minutes	After 60 minutes	1 hour after TCR	2 hours after TCR	After 30 minutes	After 60 minutes	1 hour after TCR	2 hours after TCR
Placebo	0.7 (0.5)	1.5 (0.8)	3.8 (0.8)	0.9 (0.7)	0.3 (0.1)	0.4 (0.2)	1.4 (0.2)	0.6 (0.3)
Midazolam 7.5 mg	1.7 (0.5)	2.7 (0.7)	3.6 (0.9)	2.0 (0.7)	0.7 (0.3)	0.9 (0.2)†	1.0 (0.3)	0.6 (0.2)
Midazolam 15 mg	3.9 (0.9)*	5.4 (0.9)*	5.7 (0.8)	3.2 (0.8)†	1.3 (0.4)‡	2.0 (0.4)§	2.0 (0.4)	1.0 (0.3)

* $p < 0.01$. † $p < 0.025$. ‡ $p < 0.05$. § $p < 0.001$. TCR, time to correct response.

Table 5. Digital substitution test: mean changes in score from control values.

Group	Control after 30 minutes	Control after 60 minutes	Control 2 hours after TCR
Placebo ($n = 16$)	+3.7	+5.3	+3.5
Midazolam 7.5 mg ($n = 19$)	−0.5*	−2.4†	−0.1‡
Midazolam 15 mg ($n = 18$)	−7.1†	−7.6†	−4.2§

* $p < 0.05$. † $p < 0.001$. ‡ $p < 0.025$. § $p < 0.01$. TCR, time to correct response.

Sedation. The corrected linear analogue scores and observer assessments of sedation are shown in Table 4. Midazolam 15 mg caused significant sedation at both 30 and 60 minutes ($p < 0.01$). There was also significant sedation 2 hours from the time of correct response ($p < 0.025$) when compared to placebo. Midazolam 7.5 mg caused higher sedation scores than placebo at all times, but these did not achieve statistical significance.

The observer assessments of sedation show significant sedation with midazolam 7.5 mg at 60 minutes ($p < 0.025$) and with midazolam 15 mg at both 30 minutes ($p < 0.05$) and 60 minutes ($p < 0.001$), but not 2 hours after the time to correct response.

Psychomotor performance. Patients given midazolam 7.5 mg demonstrated decreased scores in the digital-symbol substitution test at 30 minutes ($p < 0.05$), 60 minutes ($p < 0.001$) and 2 hours after the time to correct response ($p < 0.025$) (Table 5). Patients given midazolam 15 mg had markedly reduced scores at all times ($p < 0.001$, $p < 0.001$ and $p < 0.01$, respectively).

Memory. No effect on short-term memory was demonstrated in any of the patients. However, five patients who had received midazolam 15 mg and one who had received midazolam 7.5 mg volunteered complete loss of recall of the events in the operating theatre.

The commonest side effects in the postoperative period were nausea and vomiting, which occurred in one patient given placebo and two in each of the midazolam groups. The incidence of side effects did not vary between groups. More patients found midazolam helpful to them (83% with 15 mg, 63% with 7.5 mg) than the placebo (50%). However, 44% of patients in the 15-mg group did not feel sufficiently well to go home 2 hours after time to correct response, compared with 6% in the placebo group and 16% in the 7.5-mg group.

There were no significant differences in blood pressure, heart rate or respiratory rate measured

on admission, at induction of anaesthesia or at the time to correct response.

Discussion

The measurement of anxiety and sedation in patients is difficult. Maxwell[5] suggested that the linear analogue scale can provide reasonably sensitive and accurate subjective assessments of these phenomena. The sensitivity of the test can be increased by using proportional scores and the test is easy to perform and easy for patients to understand. A trained observer who makes regular assessments according to predetermined criteria, can score reproducible results on a crude scale of anxiety or sedation.[6] In this study the two methods produced comparable results at all times.

The digital-symbol substitution test is one of the most sensitive tests of psychomotor performance and also reflects an element of visuomotor performance.[7] It is simple to use in the clinical situation. Hart *et al.*[8] showed that the mental functions required for the test are particularly sensitive to benzodiazepines and, consequently, this test would be expected to provide a good assessment of the effect of the drug. Certainly this test proved the most sensitive determinant of midazolam sedative activity in this study.

It is useful to include a placebo for comparison in testing the suitability of midazolam as a premedicant, because of the placebo effect of the observer's repeated and often reassuring visits. This effect is shown in our study by the reduced anxiety scores at 30 minutes and increasing sedation scores at 30 and 60 minutes for the placebo group. Also, half the patients found the placebo beneficial.

The parenteral preparation of midazolam is formulated as a water-soluble salt but at physiological pH the midazolam base is highly lipophilic.[9] Consequently, the drug is absorbed rapidly from the gastrointestinal tract with a peak plasma concentraton 0.85 hours after dosage.[4] Systemic availability following oral administration has been measured at 41%.[4] The incomplete systemic availability is due at least in part to hepatic extraction, although incomplete absorption may contribute, and this may vary with age. Plasma levels of midazolam correlate well with pharmacological effect.[10] This would explain the limited effects observed with midazolam 7.5 mg given orally in this study. This is in agreement with Smith *et al.*[11] who found that midazolam 10 mg orally was an ineffective sedative. Absorption of the drug, however, may have been incomplete in his patients. who all had gastrointestinal disorders that warranted endoscopy.

Midazolam 15 mg did produce significant anxiolysis and sedation within 1 hour and most patients found this very helpful. Klopfenstein *et al.*[12] showed that midazolam 15–22.5 mg orally produced significantly better anxiolysis, sedation and amnesia than diazepam 10–15 mg in adults awaiting minor surgery under regional anaesthesia. The elimination half-life of midazolam is between 1.5 and 2.5 hours,[4] but the group that received midazolam 15 mg in this study showed significant sedation and alteration of psychomotor function 2 hours after the patients responded correctly. Indeed, 44.4% of this group did not feel sufficiently well to return home at this time and this is unsatisfactory for day case surgical patients. The use of thiopentone for induction of anaesthesia may have exaggerated this effect because it is a drug that is redistributed rapidly but metabolised slowly.

The study failed to demonstrate a significant amnesic effect of midazolam. This is in contrast to Klopfenstein, who demonstrated it in 14 of 20 patients.[12] This may have been due to an insensitive method of testing memory, since six of the patients did volunteer the information that their memory of events was disturbed and more may have admitted to this on questioning.

In summary, the study showed that midazolam 7.5 mg orally was ineffective premedication and that midazolam 15 mg, whilst it produced effective anxiolysis, sedation and possibly amnesia, did prolong recovery to a degree unacceptable in day case surgical patients.

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Memory of cardiac anaesthesia

Psychological sequelae in cardiac patients of intra-operative suggestion and operating room conversation

L. GOLDMANN, M. V. SHAH AND M. W. HEBDEN

Summary

Thirty patients scheduled for elective cardiopulmonary bypass surgery were interviewed pre-operatively and postoperatively to assess changes in their emotional state and recollections, both aware and unaware, of intra-operative events. A random selection of patients heard a prerecorded audio tape towards the end of bypass after they were rewarmed to 37°C. The tape contained suggestions for patients to touch their chin during the postoperative interview, to remember three sentences and to recover quickly. The interviewers were blind to the experimental condition. The experimental group touched their chins significantly more often than the control group ($p = 0.015$). Sentence recognition did not reach significance and this may be due to the small numbers and low salience of the stimuli. Seven patients (23%) recalled intra-operative events, five with the aid of hypnosis. Three reports (10%) were corroborated. Pre-operative medication ($p < 0.01$) and postoperative anxiety ($p < 0.05$) were significant predictors of those patients who reported recall.

Key words

Memory.
Complications; awareness.

The question of whether patients are aware under general anaesthesia, continues to arouse interest. Breckenridge and Aitkenhead [1] concluded that awareness (generally defined as recall) is most likely to occur with light inhalational or total intravenous anaesthesia. This may be true, but past studies have neither systematically investigated variables such as the salience of the stimuli, nor paid much attention to the manner in which the postoperative interview was conducted. Jones and Konieczko [2] recently stated that any anaesthetised patient is capable of retaining verbal and other high-level inputs in long-term memory. Therefore, it is both phenomenal awareness, that is, awareness at the time, and the consequence of memories formed during anaesthesia, that bear investigation.

Numerous studies have cited the possible harmful effects of intra-operative awareness upon postoperative recovery.[3–5] Others[6–10] have proposed the possible beneficial effects of positive suggestion made to patients under anaesthesia, such as reduction in analgesic requirements and in the number of postoperative days spent in hospital.

The present study sought to assess aware, and unaware, forms of recollection of intra-operative events in patients who underwent

L. Goldmann, MA, PhD, Psychologist, Child Care and Development Group, University of Cambridge, Free School Lane, Cambridge CB2 3RF, M.V. Shah, MRCS, LRCP, FFARCS, Senior Registrar, M.W. Hebden, MB BS, FFARCS, Consultant, University Hospital of Wales, Cardiff, Wales.
Correspondence should be addressed to Dr L. Goldmann please.

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cardiopulmonary bypass. Recall is generally understood to be a poor measure of memory so other measures, such as recognition and postoperative nonverbal responses in the form of a specific behaviour (chin touching), as well as affect, were investigated.

Method

Patient selection and pre-operative interview

Patients about to undergo elective cardiac surgery with cardiopulmonary bypass were invited to participate in the study. Information was collected from the anaesthetic and medical records about routine matters and during the course of the interviews. Psychometric data included pre- and postoperative anxiety scored by means of the Multiple Adjective Check List[11] (MACL) and the Taylor Manifest Anxiety Scale,[12] two linear analogue scales for anxiety and relaxation, and depression and hostility, measured by the MACL.

Recall of premedication, of events in the anaesthetic room and of peri-operative events was noted. The state of orientation was noted at interview. If a postoperative psychosis was suspected, a short mental status examination was administered.

Tape preparation

Patients were randomly selected without constraint for the experimental and control conditions. Tapes suitable for the particular individual were prepared that included the patient's name for each patient in the experimental group, and recorded at a very slow pace. The following text adapted from Bennett *et al.*[13] was recorded either by one of us (M.V.S.) or by another researcher: *'Mr/Mrs/Ms ... This is Dr ... You are in the operating theatre. Everything is going well. It is important that you listen carefully so that we know that you can hear and understand under anaesthesia.* (A random selection of three of six neutral sentences were read.) *When you are interviewed after your operation it is important that you touch your chin. Perhaps your chin will itch. Perhaps you may just want to touch it. It is important that you remember that I have told you to do this so that we know that you can hear and understand and remember under anaesthesia. Everything is going well and you can recover easily and comfortably.'* Patients in the control group were played a blank tape.

Postoperative interview

The postoperative interview was conducted by one of us (L.G.) accompanied either by a staff nurse or another psychologist, all blind to the experimental condition. The interview was scheduled for the 7–10th postoperative day. The reason for this was to interview the patients when they felt at their best and to minimise any residual psychological problems that resulted from the operation or stay in the intensive care unit. The interview lasted 40–90 minutes and adhered to a semistructured format. Chin touches were recorded by both interviewers. The patient was re-administered the MACL, Taylor Manifest Anxiety Scale and the visual analogue scales at the beginning of the interview.

Patients were asked what they knew about hypnosis. Misconceptions were discussed. They were then asked the questions found below and then again under hypnosis. The induction technique followed that of Elman.[14] The questions were designed to be as neutral as possible, given the ability of both hypnotised and nonhypnotised subjects to be influenced by post-event information.[15] If the patient achieved sufficient hypnotic depth, he was asked to reply to the questions using ideomotor signalling.* The following set of questions was used. Additional questions were asked as appropriate.

Do you remember being given premedication?
What is the last thing you remember before going to theatre?
What can you remember about the anaesthetic room?
What is the next thing you remember?
What is your sense of how much time had passed?
Can you recall anything that was said to you, or about you, while you were in theatre?
What can you recall feeling or hearing?
How do you remember feeling in recovery?

* Ideomotor signalling is a technique of hypnotic investigation reported by Cheek and Le Cron.[32] The subject is asked to choose one finger to signal 'yes' and another for 'no'. The patient is asked to try this several times. On many occasions, verbal and nonverbal responses contradict each other. These authors suggested that the nonverbal responses are more trustworthy as patients are often unaware of their nonverbal responses.

Is there anything you remember hearing that sounded important for you to remember?
Are you willing to remember anything that you heard or felt while in theatre?

Suggestions were made for a complete and easy recovery at the end of the hypnotic interview. Patients were told to remember only as much of the interview as would be useful or helpful. Enough latitude was included in the interview for the patients to discuss anything that they considered important. Patients were asked at the end of the interview to tick any three of the six sentences that they thought they might have heard during their operation and if the sentences reminded them of anything.

Premedication and anaesthesia

Patients received intramuscular papaveretum and hyoscine and (or) oral lorazepam. Anaesthesia was with high dose fentanyl and (or) nitrous oxide and (or) halothane. One hundred percent oxygen was given during cardiopulmonary bypass. The tape was played after the patients had been rewarmed to at least 37°C, towards the end of bypass.

Results

Thirty-three patients between 30 and 65 years of age about to undergo elective cardiac surgery with cardiopulmonary bypass, agreed to participate in the study (9 women and 24 men). The mean age was 56.3 years and the median ASA grade, 3. Of the patients who agreed to participate in the study, 30 completed it (7 women and 23 men), one died and two were too ill to be interviewed postoperatively. The average age of those studied was thus 55.6 years, and median ASA grade, 3.

Pre-operative medication

Patients either received no pre-operative medication ($n = 1$), papaveretum and hyoscine (5), oral lorazepam only (1), or oral lorazepam and intramuscular papaveretum and hyoscine (23).

Anaesthesia

Patients received either high dose fentanyl 50 μg/kg, nitrous oxide and halothane 0–1% ($n = 7$); high dose fentanyl with halothane (6), high dose fentanyl with nitrous oxide (5), medium dose fentanyl 10–20 μg/kg, nitrous oxide and halothane (4), high dose fentanyl (4), medium dose fentanyl and nitrous oxide (2), or nitrous oxide and halothane (2).

Nonverbal behaviour

There were nine patients in the control group, seven men and two women. They did not differ significantly from the experimental group except for the number of chin touches. The combined groups of patients gave a mean of 4.33 chin touches (SD 5.1). The median was 2.0 and the range, 20. The control group gave a mean of chin touches of 2.4 (SD 2.4), and the experimental group, 4.3 (SD 5.9). The difference is significant: Fisher's $F(1,28) = 5.91$, $p = 0.015$. The implied departure from normality was tested and found to be nonsignificant.[16,17] It is important to note that both groups contained a number of patients who were nonresponders. The major difference between the experimental and control groups consisted of four patients in the experimental group who exhibited dramatically high response rates.

Recall

None of the patients recalled hearing the suggestion during the operation. Several of the patients in both groups reported recall of perioperative events. It is clear from these results that suggestions made to patients under anaesthesia can influence postoperative nonverbal responses. Table 1 reports the differences between those patients who did and did not report recall.

Seven patients, all men, reported peri-operative awareness in the form of recall. These memories were both kinesthetic and auditory. Three of the reports could be corroborated (Nos. 1,3,5 below). The other four reports were less detailed and are referred to here as 'vague' recall. These seven patients did not differ significantly from the rest of the sample on any of the preoperative tests; Taylor anxiety scale (mean 11.7, SD 5.0), MACL (mean 3.0, SD 4.0) or analogue scales (mean 59.5, SD 28.5). The nonrecall group scores were as follows: Taylor, mean 9.5, SD 4.4; MACL anxiety scale, mean 2.1, SD 2.7; analogue scale, mean 58.7, SD 25.8. The patients who reported recall differed sig-

Table 1. Sex, age and medication of patients who reported and did not report recall.

	Recall (n = 7)	No recall (n = 23)
Sex (M)	7 (100%)	16 (69.6%)
Age	57.2	55.1
Premedication *		
None	0	1 (4.3%)
Papaveretum and hyoscine	4 (57.1%)	1 (4.3%)
Lorazepam	1 (14.3%)	0
Lorazepam, papaveretum and hyoscine	2 (28.6%)	21 (91.3%)
Anaesthetic agents		
High dose fentanyl (> 50 μg/kg)	5 (71.4%)	17 (73.9%)
Medium dose fentanyl (10–20 μg/kg)	1 (14.3%)	5 (21.7%)
Nitrous oxide	5 (71.4%)	15 (65.2%)
Halothane	6 (85.7%)	13 (56.5%)
Visual analogue postoperative (mm)		
Relaxation	82.9	78.6
Anxiety**	38.6	17.4

* $p < 0.005$; ** $p < 0.05$.

nificantly from the nonrecall group with respect to postoperative anxiety, as measured by the visual analogue scale (nonrecall group, mean 17.4, SD 22.3; recall group, mean 38.6, SD 36.2), $F = 3.9$ significant at $p < 0.05$. The linear analogue scores did not depart significantly from normality.

Almost every patient who said that they could recall a peri-operative event showed some kind of abreaction during the interview; sweating, crying, fidgeting, or wringing hands. Only half of the patients who said they could not recall anything showed the same kind of behaviour and, if they did, with much less intensity. This difference was not significant. An analysis of variance was conducted and the following variables shown to significantly differentiate the recall and nonrecall groups: pre-operative medication, $F(1,28) = 9.8$, $p = 0.003$; and postoperative anxiety, $F = 3.97$, $p = 0.05$. Eighty-six percent of patients who reported recall received halothane, versus 56% of nonrecallers. This figure approached but did not reach significance.

One question concerns the reliability of the anxiety measures. There was a significant correlation between pre-operative measures of anxiety (Taylor and MACL, Pearson's $r = 0.32$, $p < 0.03$; linear analogue and MACL, Pearson's $r = 0.62$, $p < 0.01$). Some of these patients looked very anxious during the pre-operative interview, while their anxiety scores appeared low. Reports from their families and other patients supported this impression. It is possible that the Taylor and MACL are quite transparent, and the linear analogue scales, less so. Many patients, we believe, tried to appear calm. It was our impression, and that of the staff and members of the patients' families, that these patients wanted to be seen as courageous. The postoperative measures of anxiety were presented before the hypnotic interview and, therefore, it is unlikely that the information that came to light as a result of hypnosis influenced these scores. As expected, all measures of anxiety showed significant reductions between pre-operative and postoperative testing ($p < 0.01$).

Gender. Four patients, all women (Chi squared, $p < 0.0003$), suffered from transient postoperative psychoses. They were disoriented in time, place and environment. These women were interviewed several times over a period of days. Only the results of the last interviews are included. The women, as a whole, scored higher on anxiety, hostility and depression than the men on the postoperative MACL. Their scores approached significance. It is difficult to say whether this effect is related to gender alone. The women occupied single, two-bedded and, more rarely, four-bedded rooms. The men occupied an eight-bedded ward. The atmosphere on the eight-bedded ward was often quite jolly, while the atmosphere in the women's rooms was often subdued. The severely decreased social

contact both between women and between women and staff may have exaggerated, or prolonged, postoperative psychoses.

Cognitive functioning. Fifteen patients noted some problems with their vision and 12, with cognitive functions. Three patients noted that after an interval of more than a week, they continued to have difficulty completing the crossword puzzles in the newspapers. This was a skill that each of them had prior to their operation. It is possible that this kind of test may be a sensitive instrument to test postoperative cognitive dysfunction. All of the patients underestimated the durations of their operations.

Dreams. Three patients reported dreams which they thought were suggestive of their operations, two in the form of persistent nightmares. The contents of these dreams were as follows.

A 64-year-old woman dreamed of being instructed in a schoolroom. She said that she could hear people around her talking, but did not understand what they were saying.

A 43-year-old man had persistent dreams of being in an operating theatre.

A 49-year-old man said he could not remember his dreams but they left him feeling sad.

Recall. Abbreviated transcripts of the seven interviews of patients who reported recall of perioperative events follow.

Patient L. This patient did not recall his premedication or journey to the operating suite. He remembered nothing until 'the operation must have been on'. He reported under hypnosis that he felt he was in some kind of workshop with lots of clanking metal. He said of the anaesthetist, 'He must have been asking me to swallow a pipe. Funny, in my mind I was going to say to him, 'I can't eat all this'. It was like a hose, sort of crinkly.' He also said that he thought he heard his name called by a young girl with a foreign accent (the message on this tape was dictated by a woman with an Indian accent).

Patient W. This patient reported under hypnosis that he heard his name spoken during the operation and a man's voice that told him to remember to do something, which he could not at present remember. Using ideomotor signalling he said that he did not want to remember details of his operation. He touched his chin repeatedly (20 times) during the hypnotic interview. He also became agitated and distraught.

Patient E. This patient, both in the ICU and while under hypnosis, repeatedly asked what 'cross-clamping' meant. He felt certain that it was something he had heard in the operating room. He reported under hypnosis that, during the operation, he thought he heard a man's voice telling him something. He also stated that he 'had a funny sensation while I was there. I could picture it and I could feel it. They were cutting my leg with a thin razor just under the skin and I could feel the sensation and it was a funny sensation. (Draws a line up his leg from the calf past the knee.) While hearing these voices I had the funny feeling that I wasn't going to pull through. Something seemed to be happening in the back of my mind as if something was going to happen, as if there was going to be a mistake. A terrible feeling, I wanted to get away from it.' When ideomotor signalling was used, the patient indicated that he did not want to remember any more. The patient looked flushed and uncomfortable and spontaneously terminated the hypnosis. He was amnesic for events which had occurred under hypnosis. (The term cross-clamping may have been used. The patient described accurately the procedures performed during the operation.)

Patient A. This patient was a fair hypnotic subject and indicated that he was very willing to remember intra-operative events. While he reported under hypnosis events which he thought occurred during the operation, he said that his arm had become very cold. (It was cold to the author's touch and the patient shivered during the interview.) He reported that he heard people talking and this included someone with a foreign voice. He said that he now felt his leg and arm twitching, and his left leg hurt as if it had just been cut. He also said that he could smell gas. He began to sweat and squirm in his chair and spontaneously brought himself out of hypnosis. The patient looked upset and said that he became frightened when he heard the words 'cerebral haemorrhage'. He asked me what that meant and what it had to do with him. He reported that he had not heard the words before and wondered if he had heard them correctly.

Patient T. This patient, when he heard that the author wanted to interview him about his operation, made the author promise not to record the session or tell anyone about it. He later reported that he had been afraid to appear ungrateful and that he would be treated poorly on the ward as the result of what he was about to tell me. Later, after he had been reassured that what was said would not implicate him, he agreed to restate parts of the interview and allow a recording to be made. The patient spontaneously reported (not under hypnosis) that he had felt darkness around him and felt as if he was in a state of suspended animation. He listened to a discussion about Austin cars. (He collects antique cars and therefore this would be salient.) He then heard a rather angry voice, which he believed to be the anaesthetist's, saying 'Don't tell me what to do. I know what I am doing!' This alarmed him. He then heard a foreign voice followed by a 'deep, strong commanding voice' which he believed to be the surgeon, saying the patient 'was something' followed by a list of numbers. During this time he tried very hard to move and to change his breathing 'so that they would put me deeper'. The patient said he was concerned not about the fact of being aware, but about the argument that he felt was going on around him. (The argument and the discussion about cars were confirmed.) No additional information was found with the use of hypnosis.

Patient B. This patient was a good hypnotic subject and showed no recall of intra-operative events. Just

prior to the termination of the interview, the patient said he was surprised that he had been unable to recall anything because he felt quite willing. He asked to be rehypnotised and again he answered 'no' when asked if he was willing to recall peri-operative events. This was again discussed with him and again he expressed his willingness to recall. A final attempt was made and he responded with a 'yes' signal. He indicated that he heard two groups of three people and indicated their placement. (This was correct.) He also indicated that he felt cold and had pains in his left arm and leg. He heard numerous discussions, all very indistinct: 'something about holidays and time, and schedules.' He began to sweat and cry and the interview was brought to a close.

Patient C. This patient was also a good hypnotic subject who expressed great fears of remembering anything under hypnosis but said that he was willing to try. He reported spontaneously and under hypnosis that he remembered 'something in my mouth and people talking around me.' Only during hypnosis did he report that he had wanted to talk, but felt unable. He also mentioned feelings of calm, ease and comfort.

Discussion

These results suggest that patients who receive anaesthesia for cardiac surgery show aware and unaware recollection of peri-operative events. They recollect both auditory and kinaesthetic events. The memories subject to verbal recall varied in their detail and in the degree to which they could be corroborated. Some of the reports do appear dream-like, but none of the patients reported that they felt they had been dreaming during the operation. It is possible that some of the reports may have been influenced by events that occurred pre- or postoperatively.

Several of the reports were accompanied by strong affect. When patients with specific recall were combined with those who had vague (uncorroborated) recall, this group showed significant differences from the rest of the sample. The group received a lighter premedication, were more anxious postoperatively and had a tendency to receive more halothane. There was a significant difference between experimental and control groups in the number of chin touches. Sentence recognition was better in the experimental group but did not reach significance. This is most probably due to the small number and low salience of the sentences.

Surgical and anaesthetic lore is rich in anecdotes that concern awareness. The most common explanations are equipment failures, light pre-operative medication or insufficient anaesthetic. Case studies generally report incidents of high salience, while most prospective investigations, for obvious reasons, have relied upon recall and stimuli of low salience; words, music or stories.[18–20] These latter studies have found a low incidence of recall. When hypnotic techniques have been used with highly salient stimuli and good hypnotic subjects, a high incidence of recall has been reported.[21] This may be due to the ability of hypnotised subjects to reinstate state-dependent variables, establish rapport or loosen their associations. Hypnotised subjects are more apt to fabricate than nonhypnotised subjects. However, as patients who recalled intra-operative events became quite anxious and as recall is not a desirable outcome, we are fairly certain that patients were not endeavouring either to mislead us or to adopt a compliant role by presenting false information.

Two factors are important in understanding the incidence of awareness: the salience of the stimulus, and the methods used for detection. Salience, defined as novelty, emotionality or surprise, has been associated with both orienting responses (ORs)[22] and increased recall.[23] Galvanic skin responses have been elicited in spontaneously breathing patients who received an inhalational anaesthetic, in response to surprising auditory stimili.[24] Low-salience stimuli heard under anaesthesia are unlikely to produce ORs or recall.[25] Salient stimuli (for example, a mock peri-operative crisis[21]) may produce both ORs and a high incidence of recall. It is worth noting here that Levinson[21] cited electroencephalographs as indicators of orienting responses and these occurred prior to the enactment of the peri-operative crisis.

While recall has been the preferred method of assessing awareness, it is the least sensitive. Patients may show the effects of learning through recognition or nonverbal responses even when they have been unable to recall peri-operative events.[13,26]

Bennett *et al.*[13] reported highly significant results when patients who received various premedications and anaesthetics, were played a personalised tape during their operation which asked them to pull on their ear during a post-operative interview. None of the patients recalled the instructions, although there were increases in both the number of earpulls and attention paid to the ear. Our findings support those of Bennett *et al.* Similar to the patients in Bennett's study, none of our patients recalled the suggestions.

The question remains as to why the patients thought the instruction sufficiently salient as to be remembered. We believe that the message was given additional weight for the following reasons. Patients were carefully interviewed preoperatively, and understood that taking part in the study might be of possible benefit to them. Their name was recorded on the tape and the suggestion was phrased in a 'hypnotic-like' manner. Additional suggestions were made for their comfort. Possibly the message was unusual or surprising.

Investigations of priming effects and blindsight conditioning, as well as of amnesic patients, support the notion that conscious or phenomenal awareness is not necessary for learning to occur. Learning may occur without the patient's ability to state how and when.[27–29] Recall which tests declarative memory (the patient's ability to construct a verbal description) is not as sensitive as tests of procedural memory, such as the ability to perform a task. For example, patients with Korsakoff syndrome may perform as well as normal subjects when memory tasks are designed to test less intentional forms of memory, such as spelling or recognition of a degraded word.[30] This led Eich[31] to conclude that methods of detecting memory for unattended events (such as those that occur while asleep, while selectively attending to something else, or while under anaesthesia) are unlikely to access memory if they rely upon intentional remembering.

The inability of patients to recall events does not mean that they have not been aware. Awareness under anaesthesia may result in behaviour changes too subtle to be noticed by hospital staff. The events that patients recall, whether or not they can be corroborated, are likely to be highly salient and associated with high postoperative anxiety. Changes in anaesthetic technique, or increased premedication, may decrease aware forms of remembering, leaving recollections outside of verbal recall intact.

None of the techniques of cardiac anaesthesia, high or medium dose fentanyl, with or without nitrous oxide and halothane, appears able to prevent registration of suggestions made to patients during bypass. High dose fentanyl anaesthesia tends to be better at preventing patients from recalling (or having the feeling that there are memories to be recalled) salient intraoperative conversation.

The observation that recallers as a group received halothane more often than nonrecallers (6/7 *versus* 13/23) needs to be explained. It is common practice when dealing with labile cardiovascular systems (CVS), to give a minimum of anaesthetic agent since most are myocardial and circulatory depressants. When these agents are used cardiovascular responses occur and there is a significant lag period before an adequate depth of anaesthesia is achieved. This is particularly true at the start of surgery and at withdrawal of cardiopulmonary bypass.

Fentanyl, even at doses >50 μg/kg and when combined with a heavy premedication, causes relatively little cardiovascular response. Therefore a full anaesthetic dose may be given at induction, enough to provide anaesthesia and CVS stability for the whole operation without the need for further supplementation, and whilst 100% oxygen is used.

Thus an anaesthetic technique that is based primarily upon inhalational agents, with small doses of intravenous analgesics, becomes inadequate when the inhalational component is absent, and may be more likely to lead to registration of information and recall. In no patient were inhalational agents given during bypass. Therefore, towards the end of bypass, at normothermia, those patients who had previously received nitrous oxide, oxygen and halothane were unanaesthetised. It is surprising that more of these patients did not have recall for events during this period.

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Retention of auditory information presented during anaesthesia

A study of children who received light general anaesthesia

P. J. STANDEN, W. R. HAIN AND K. J. HOSKER

Summary

Surgical procedures that involve a local anaesthetic block are often accompanied by light general anaesthesia. It is possible that under these circumstances, the patients are more likely to register auditory events while apparently unconscious. Two groups of children were exposed to auditory stimuli during surgery; one group received a lighter level of anaesthesia than the other. Retention of the stimuli was tested using a cued recall technique, and the performance of the two experimental groups was compared with a control group which had not been exposed to the material but was tested in the same way. The light anaesthesia group retained more items than did the other two groups but this difference was significant ($p < 0.05$) only when compared with the other experimental group. This is not very strong evidence of auditory registration, but a greater effect might be found with exposure to emotionally significant material. It is suggested that patients should be protected from unfortunate theatre conversation.

Key words

Complications; awareness.

The increasing use of local and regional anaesthetic techniques to provide analgesia during and after general anaesthesia for some surgical procedures, especially in children, results in the need to maintain only a very light level of anaesthesia. Even during surgical anaesthesia, some patients have been shown to retain some auditory material when the method of testing is sufficiently sensitive.[1] The incidence of spontaneous recall of material to which patients are exposed during anaesthesia is low, but such material can influence later behaviour either positively[2] or negatively.[3] It is possible that auditory material is more likely to be registered at lighter planes of anaesthesia.

The use of a caudal or epidural block is helpful in children who undergo elective surgery below the level of the umbilicus.[4,5] However, because the concentration of inhaled anaesthetic agent necessary to maintain immobility and apparent unconsciousness is reduced, it is possible that the patient may be rendered more receptive to auditory stimuli such as conversation in theatre.

The present study was designed to investigate this possibility by exposing patients to auditory material during surgery. During recovery, responses to cued recall were compared in two groups of children who received different concentrations of halothane.

Patients and methods

Background

The method of testing must be sensitive in order to elicit any memory of experiences registered during anaesthesia. Millar and Watkinson[1] used

P.J. Standen, BSc, PhD, Lecturer in Behavioural Sciences, Behavioural Sciences Section, Department of Psychiatry, W.R. Hain, MB, BS, FFARCS, Consultant, Department of Anaesthesia, K.J. Hosker, BSc(MedSci), Medical Student, Queens Medical Centre, Nottingham.

a recognition test for material to which subjects were exposed during surgery, since recognition is a more efficient means of retrieval than free recall. However, cued recall (for example, showing subjects the first three letters of a word) has been shown to be a more successful method of eliciting memories from amnesic patients.[6]

If the memory trace is weak and recall is cued using the name of the category to which the item belongs, subjects produce incorrect answers as guesses; these are usually the most 'dominant' responses, i.e. the ones most likely to be produced when subjects are asked to name words which fit a particular category.[7]

If subjects were exposed during light anaesthesia to stimulus words of low dominance and registered this material then, when questioned afterwards using cued recall, they would produce these low-dominance words more often than would patients for whom there was no registration of auditory material during anaesthesia.

Information on the dominance of category words exists for adults[8] but no norms exist for children. Therefore a pilot study was carried out on 50 children aged between 5 and 13 years to determine suitable stimulus words and a series of cues for testing recall. Six stimulus words were chosen because of the length of time required to test for recall. Stolzy *et al.*[9] found evidence of retention using six words; Millar and Watkinson[1] used eight words. The six stimulus words chosen each came from a different category (e.g. food, animal) and were selected because, when children were asked to produce words which fitted a particular category, these words were not the most dominant but were familiar, i.e. all children could produce these words if given sufficient cues. The six words used were: banana, camel, parrot, scarf, tractor, wall.

A series of cues was also chosen such that the first for each word was its category and the second, its initial letter. For these two cues there was always an alternative answer to the stimulus word. Subsequent cues referred to more specific characteristics, e.g. 'You find it on the farm' (stimulus word: tractor).

The six words were recorded onto a tape eight times. The serial order was varied across each presentation of the words to reduce primacy and recency effects. The words were recorded at a rate of one per 2 seconds and were preceded by an instruction to the child to listen, using his own christian name. The tape was recorded using the experimenter's voice and lasted 2.25 minutes.

The retention test took the form of a game whereby the child had to guess the word of which the experimenter was thinking, with the help of a series of cues.

Patients

Permission to conduct the study was obtained from the University Hospital ethical committee. Parental consent for the investigation was given in all cases. No suggestion was made that any child would be anaesthetised inadequately.

Forty-one children (27 male, 14 female) aged between 5 and 13 years undergoing minor and orthopaedic surgery, were assigned randomly to the high or low halothane group with restraint such that the groups were matched for age and sex. The mean ages in years for each group were: high, 8.4; low, 8.6.

Methods

Premedication was given to 39 children. It consisted of either diazepam 0.5 mg/kg (but not more than 20 mg) or trimeprazine 2 mg/kg with or without droperidol 0.2 mg/kg. Induction of anaesthesia was usually by thiopentone 4.5–6.0 mg/kg intravenously or, in five cases, by mask inhalation of halothane, briefly up to 5%, in nitrous oxide and oxygen (2:1).

A local anaesthetic block was instituted after induction of anaesthesia. Twenty-three children received a caudal block using 0.5% bupivacaine ([age (years) + 2] ml) and nine received a penile block using 0.5% bupivacaine, 1 ml per 3 years. All patients breathed halothane 1.5% (high) or 0.5% (low) for 15 minutes before the tape was played through headphones. After the recording had been played, all children breathed 0.5% halothane unless a clinical indication arose that necessitated a greater concentration.

In three patients no local block could be performed. They breathed 1.5% halothane throughout the anaesthetic period.

As soon as the patient had recovered sufficiently after surgery to be able to converse, each was tested by the investigator using the cued recall technique. It was impossible to test at a set time postoperatively because patients usually slept through the night following afternoon surgery, and could not be tested until

the following morning. After morning surgery, patients could be tested late in the afternoon. The investigator was not aware of the experimental group to which the subject belonged.

Initially, the child was instructed 'Tell me all the things you can think of that . . .' (description of the word, e.g. 'you can eat'). If the correct word was produced at this stage, the child was not stopped; when words were no longer volunteered, the child was told 'That's good'. This procedure allowed a rate of word production to be recorded, the importance of which is discussed later. If the target word was not elicited by the first cue the child was told 'I'm thinking of another one that you haven't said yet. It begins with . . .' (initial letter). For this and subsequent cues the child was stopped when the correct word was produced and told that this was the correct response. In order to retain motivation it was necessary to reward the children with feedback and this precluded obtaining a measure of confidence of their guesses. For each child it was noted whether the correct word was produced, the number of incorrect words produced before the stimulus word, and the number of cues required before the word was produced.

The time interval between the exposure to the material and testing was noted. The mean time interval for those operated on in the morning was 4.9 hours. It was 19.6 hours for those who went to theatre in the afternoon.

In order to control for the frequency with which the stimulus words are produced spontaneously, the cued recall technique was carried out in exactly the same way on 20 children (15 male, mean age 9.0 years) during recovery from similar operations but without exposure to the test material.

Results

There were no differences between the two experimental groups in respect of the type of operation, type of local block, premedication, induction agent, time of day of operation, time of day of testing and time interval between exposure and testing. The control group was similarly matched.

For the performance on cued recall, each subject received four scores: the number of correct words produced out of six; the median of the number of incorrect words produced for each of the six stimulus words (if the subject failed to produce the stimulus word after all cues had been given, an arbitrary high score was given for that word); the median of the number of cues required to produce each stimulus word; and the median of the number of words produced to the first cue for each stimulus word. Medians and ranges for these scores are shown in Table 1.

Using a Mann–Whitney U test to compare each group with the other two, no significant differences were found in the number of words produced to the first cue, i.e. no group increased its chances of finding the correct word simply by increasing the number of words produced. Neither was any difference between groups found in respect of the number of incorrect words produced before the stimulus word, or the number of cues required to elicit the word.

When the numbers of stimulus words produced correctly were compared, the low halo-

Table 1. Scores for performance on the cued recall task for the three groups 0.5% (low) halothane, 1.5% (high) halothane and control.

	Halothane 0.5%		Halothane 1.5%		Control	
Score	Median	Range	Median	Range	Median	Range
Number of words produced correctly	5.79	5–6	5.33	3–6	5.73	4–6
Number of incorrect words produced for each of six stimulus words	7.58	5.00–12.50	6.75	5.00–11.00	7.42	4.50–11.50
Number of cues	3.09	2.10–3.83	3.09	2.25–5.50	3.34	2.00–4.17
Number of words produced to first cue for each of six stimulus words	5.42	3.50–9.50	5.06	3.00–9.00	5.25	2.00–8.50

thane group produced significantly more than the high halothane group ($U = 138$, $p < 0.05$). However, neither group was significantly different from the control.

Discussion

An assumption was made that if the children who received a lighter anaesthetic registered the auditory material, then these children would produce more stimulus words than the control group. In addition, if the deeper level of anaesthesia was sufficient to block registration, then this group would perform no differently from the control group. Consequently, the pattern of results is difficult to interpret.

One possible explanation is that the group which received more halothane took longer to regain full consciousness and, consequently, their retrieval of the information was suppressed. However, their performance in terms of number of words produced to the first cue, suggests that they were no more sedated than either of the other two groups. This measure also rules out the possibility that one group was more likely to produce the stimulus words by chance purely because they were producing more words.

The problems of testing for registration of auditory stimuli presented during anaesthesia have been identified by other investigators,[10] and are increased in this age group. With one exception[11] there have been no positive reports in children. Hutchinson[12] excluded children under 16 from her study because of uncertainty of accurate communication. The present study has the advantage of using a sensitive test of recall which increased the chances of detecting a memory trace awareness. However, the material used comprised single words with no emotional significance. Meaningfulness of material may affect its registration and retention;[3] thus the present finding could be evidence of a weak memory for information which lacks emotional significance for the recipient. Following Levinson's[13] findings, staging a mock surgical crisis is now considered unethical. Thus methods of increasing the meaningfulness of the material are limited. In the present study it was hoped that use of the patient's name in the tape recording, and instructions to listen, might increase the relevance of the message.

The only measurement that suggested a difference between groups was the number of stimulus words produced correctly. The median for each group, including controls, approached the total number of words presented on the tape recording. The difference between the groups might have been amplified had stimulus words of a much lower frequency been employed.

The strict control of anaesthetic concentrations in the high and low halothane groups did not apply to the control group and it is not necessarily appropriate to assume that identical anaesthetic techniques were employed for these patients. However, enquiry suggests that little difference existed in this regard. Nevertheless, the absence of statistically significant differences between either experimental group and the control group must be interpreted with caution. Future studies should include a more formally constructed control group, with blank tape or white noise relayed through headphones. Individuals who test for recall should also be unaware of whether subjects were within an experimental or control group.

The probability of detecting a difference between the groups is small because, although depth of anaesthesia is suspected to be related to the probability of auditory perception,[14] individual patient variation may be a more important factor than the concentration of anaesthetic agents.[15] However, until further work can be completed to overcome the limitations of this study as regards frequency of stimulus words employed and the nature of the control group, the possibility that auditory material was registered in the light anaesthetic group cannot be excluded. When the potential benefits of a light general anaesthetic supplemented by a local analgesic block are desired, it may be prudent to protect patients from unfortunate conversation in theatre.

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Should air–oxygen replace nitrous oxide–oxygen in general anaesthesia?

H. MOSELEY, A. Y. KUMAR, K. BHAVANI SHANKAR, P. S. RAO AND J. HOMI

Summary

The use of compressed air–oxygen mixtures to replace nitrous oxide–oxygen in general anaesthesia was investigated in 378 patients. There were neither prolongations of recovery time nor instances of awareness under anaesthesia. The cost of general anaesthesia using compressed air–oxygen was about half that for nitrous oxide–oxygen mixtures.

Key words

Anaesthetic gases; nitrous oxide.
Gases, nonanaesthetic; air.

The Queen Elizabeth Hospital, like many in the Caribbean, spends large sums of money annually to purchase medical gases, chiefly oxygen and nitrous oxide. Nitrous oxide is used mainly for its analgesic properties and as a carrier gas for volatile anaesthetic agents. There are few specific indications for the use of nitrous oxide with the development of balanced anaesthesia and reliable, potent, intravenous agents. However, the use of oxygen alone may result in symptoms of oxygen toxicity and reduced functional residual capacity if anaesthesia is prolonged. Teeple and Pavlov[1] reported the use of compressed air as a diluent for nitrous oxide and oxygen, to prevent retrolental fibroplasia, and Jones and Hendershot[2] described the use of compressed air and oxygen mixtures with closed gas-containing spaces, in anaesthesia for premature infants. Garg *et al.*[3] reported the use of compressed air in anaesthesia when there were no other anaesthetic gases available. The present study was designed to test the effectiveness and cost of replacing nitrous oxide with compressed air.

Methods

All patients scheduled for elective surgery in two of our operating theatres during the period 3 September to 30 October 1985 were subjects of the study. The physical status of the subjects ranged from ASA grades 1–4. The study was approved by the medical ethics committee of the hospital.

Anaesthetists were assigned to the two operating theatres on a rota which was not specially arranged and no special instructions as to anaesthetic technique were given. They were asked to complete a form giving details of

H. Moseley, FFARCS, Lecturer in Anaesthesia and Intensive Care, A.Y. Kumar, MD, Consultant, K. Bhavani Shankar, MD, Consultant, Department of Anaesthesia, Queen Elizabeth Hospital, Barbados, P.S. Rao, PhD, Consultant Statistician, West Indies Sugar Cane Breeding Centre, Barbados, J. Homi, FFARCS, Professor, Department of Anaesthesia and Intensive Care, University of the West Indies, Mona, Jamaica.

anaesthetic technique that included drugs, volatile agents and volume of gases (flow and duration) used for each case.

The operating theatres are equipped with pipelines for oxygen, nitrous oxide and compressed air. Oxygen and nitrous oxide are delivered in H-size cylinders (ASA), of capacity 5900 and 15 800 litres, respectively. The compressed air is supplied from an Ohio Medical air compressor (Model 4900-600) and a Bird low flow oxygen–air blender was used to supply a known concentration of oxygen to the Boyle's machine. This concentration was checked frequently by means of a calibrated Ventronics polarographic oxygen analyser (Model 5570) with a Model 5580 sensor. The oxygen Rotameter was used for the compressed air–oxygen mixtures after precalibration using spirometry had shown the error to be not greater than 5%. Care was taken to ensure that the nitrous oxide supply was disconnected from the anaesthetic machine when compressed air–oxygen mixtures were used.

In one operating theatre, anaesthesia was administered using nitrous oxide and in the other, compressed air was substituted. This arrangement was rotated at weekly intervals between the theatres to ensure uniformity among the groups. The vaporizers used were coded and each was filled from a similarly coded bottle of halothane.

The patients were considered in two groups: group A received compressed air and oxygen, and group B, oxygen and nitrous oxide. All patients were admitted to the recovery room together with patients from the other theatres not in the study. The nurses, who were not aware of the study, were asked to note carefully the time at which every patient was fully awake and able to answer to their name, and the duration of stay in the recovery room. All patients from the two operating theatres in the study were interviewed by a trained interviewer who had no knowledge of the reason for the study. A questionnaire was used in which questions about awareness were concealed among others about the minor complications of anaesthesia.

Student's *t*-test was used to evaluate the statistical significance of the difference between the values for mean duration of anaesthesia, mean time for recovery and mean duration of stay in the recovery room in groups A and B. The Chi squared test was used to evaluate the statistical significance of the results from the questionnaires.

Results

A total of 378 cases were studied, 180 in group A and 198 in group B. The total duration of anaesthesia was 197 hours 23 minutes in group A, and 207 hours 52 minutes in group B.

Table 1 shows the mean duration of anaesthesia, the mean time for recovery and the mean duration of stay in the recovery room in each group. There was no statistically significant difference between the groups.

Interviews were conducted with 300 patients; 78 cases were either children who were not competent to answer questions, or patients who could not be traced for interview. There were no instances of awareness at the time of surgery, either from spontaneous complaints or on direct questioning. Six patients, three in each group, admitted to dreams of a pleasant nature during recovery from anaesthesia. There was no statistically significant difference in the number of complaints between the groups.

The total cost in group A was US $913.73, or US $5.08 per case, and in group B was US $1965.12, or US $9.92 per case (Table 2).

Table 1. Duration of anaesthesia, recovery and stay in recovery room.

	Compressed air–oxygen (Group A)	Nitrous oxide–oxygen (Group B)	p
Mean (SEM) duration of anaesthesia, minutes	65.79 (3.77)	62.9 (3.9)	NS
Range, minutes	5–255	5–318	
Mean (SEM) time for recovery, minutes	42.98 (3.52)	42.16 (3.66)	NS
Range, minutes	0–242	0–262	
Mean (SEM) duration of stay in recovery room, minutes	151.93 (6.23)	144.49 (6.71)	NS
Range, minutes	15–620	22–442	

NS, not significant.

Table 2. Cost effectiveness (US $).

Drug/agent	Compressed air–oxygen	Nitrous oxide–oxygen
Thiopentone	26.87	26.87
Pethidine	15.31	13.75
Morphine	16.74	9.02
Promethazine	24.21	26.79
Diazepam (Valium)	6.46	4.04
Flunitrazepam (Rohypnol)	8.64	11.52
Midazolam (Hypnovel)	50.83	48.33
Suxamethonium	73.14	104.35
Pancuronium	82.17	85.39
Tubarine	176.52	164.75
Gallamine	0.78	–
Halothane	224.09	178.67
Oxygen	147.36	216.36
Nitrous oxide	–	1075.28
Compressed air	60.61	–

Discussion

The study clearly shows the great savings available by the use of compressed air instead of nitrous oxide in general anaesthesia. Analysis of the results shows that the major saving was made by substitution of air for the more expensive nitrous oxide, and there was also a 32% reduction in the cost of oxygen used. There is very little difference in the pattern of anaesthesia compared with the use of other drugs; therefore, it is not surprising that there was no significant difference in the times for recovery or the stay in the recovery room between the two groups.

Nitrous oxide was previously thought to be non-toxic but there is an increasing literature which describes the toxic effects of nitrous oxide. Saidman and Hamilton[4] include in their list of the disadvantages of nitrous oxide, expansion of compliant spaces, pressure increases in non-compliant spaces, diffusion hypoxia and inadvertent delivery of hypoxic mixtures. Seyde and his colleagues[5] have shown that the addition of 70% nitrous oxide to a stable background of approximately 1 MAC halothane anaesthesia, resulted in a decrease in cardiac output and major alterations of blood flow to several vital organs in rats, and Banks *et al.*[6] showed that nitrous oxide is capable of oxidising vitamin B_{12} from the Cob-I-alamin form to the inactive Cob-II-alamin form. It has also been shown that in commonly used anaesthetic concentrations, nitrous oxide can cause inactivation of enzyme methionine synthase in animals[7] and in man,[8] and in low concentrations for long periods in animals.[9] Amess and his colleagues[10] showed that exposure to nitrous oxide, through decreased activity of methionine synthase, can lead to impaired production of DNA when assessed by the deoxyuridine suppression test. It also caused an abnormal deoxyuridine suppression test in 85% of critically ill patients admitted to intensive care who received nitrous oxide for less than 2 hours, and in 95% of patients after 2–4 hours of exposure.[11] Baden *et al.*[12] showed that chronic exposure of pregnant animals to nitrous oxide, reduced both maternal and fetal methionine synthase activity. They pointed out the need to study the possible effects on the human fetus following Caesarean section under nitrous oxide anaesthesia.

Both these and epidemiological studies[13,14] seem to have direct implications not only for patients who are anaesthetised with nitrous oxide, especially those who are very ill, but also for those theatre personnel, particularly pregnant women, who endure chronic exposure to low dose nitrous oxide due to theatre pollution.

The use of compressed air–oxygen mixtures improves safety under general anaesthesia because it greatly reduces the possibility of hypoxia that may arise from accidents with machines or pipelines, and renders low-oxygen alarms obsolete.

We recognise that there are some cases where the use of nitrous oxide is indicated for rapid, easily reversible anaesthesia and analgesia. However, we agree with the recommendation of Eger,[15] that nitrous oxide be treated like any other drug and used only where its use is specifically indicated. If this were done, there would be a significant reduction in the cost of anaesthesia at present prices compared with the routine use of nitrous oxide.

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Nausea and vomiting after prostaglandins in day case termination of pregnancy

The efficacy of low dose droperidol

J. M. MILLAR AND P. J. HALL

Summary

The antiemetic effects of low dose droperidol (0.25 and 0.5 mg) and a placebo were compared in patients who had received prostaglandin for day case termination of pregnancy. The incidence of nausea and vomiting was high. Low dose droperidol significantly reduced postoperative nausea and vomiting without any delay in immediate recovery or discharge home ($p < 0.05$). Droperidol 0.25 mg was equally effective as an antiemetic, as 0.5 mg.

Key words

Vomiting; nausea, antiemetics.
Anaesthetics, intravenous; droperidol.

Prostaglandin pessaries are increasingly being used to facilitate termination of pregnancy, as they reduce bleeding and the force needed for mechanical dilatation of the cervix, particularly in nulliparous patients.[1–4] The high incidence of nausea and vomiting associated with their use is apparent clinically, but has largely gone unremarked in reports of their use. This is yet another factor which makes women who present for day case termination of pregnancy, especially prone to nausea and vomiting.

Low dose droperidol has been used as an antiemetic with promising reports of its effectiveness coupled with a lack of postoperative sedation, which make it suitable for day surgery.[5,6] This study aimed to establish the incidence of nausea and vomiting in patients who received prostaglandins and to assess the value of two different low doses of droperidol in the prevention of this, without any delay in safe discharge home.

Methods

One hundred and fifty patients who presented for day case termination of pregnancy gave informed consent for the double-blind study which was approved by the Central Oxford Research Ethics Committee. All were aged over 16 years, assessed pre-operatively as ASA grade 1 or 2 and were not taking antiemetics or drugs with a possible interaction with droperidol.

Prostaglandin E_2 pessaries 10 mg were given pre-operatively. No sedative or narcotic premedication was given. The patients were assigned randomly to one of three groups to receive intravenously either sterile water, droperidol 0.25 mg or droperidol 0.5 mg. The hospital

J.M. Millar, MB, ChB, FFARCS, Consultant, Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford OX2 6HE, P.J. Hall, MB, BS, FFARCS, Registrar, Royal Children's Hospital, Flemington Road, Parkville, Victoria, Australia.

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pharmacy prepared identical, randomly numbered ampoules that contained the test dose in 0.5 ml.

A standard general anaesthetic was given: alfentanil 500 mg followed by lignocaine 10 mg to prevent pain on injection,[7] methohexitone 1.5–2 mg/kg followed by maintenance with 33% oxygen in nitrous oxide, 1–2% enflurane and spontaneous ventilation via a Bain system. Increments of methohexitone were given as necessary. The test solution, 0.5 ml, was given intravenously immediately after induction. The electrocardiogram (ECG) was monitored continuously and blood pressure recorded pre-operatively and at 5-minute intervals throughout the procedure. The time taken for the procedure was recorded.

The times taken to eye opening and giving correct date of birth on command postoperatively were recorded. Paracetamol 1 g and metoclopramide 10 mg were routinely prescribed for postoperative pain and nausea, and were administered at the discretion of the recovery staff in the usual way.

Assessment of nausea and vomiting. The ethical committee required that the patients were informed that the purpose of the study was to investigate the prevention of nausea and vomiting. Any bias introduced by this should be uniform throughout the groups. Nausea was enquired about pre-operatively, and retching or vomiting were noted. Retching, vomiting and spontaneous complaints of nausea postoperatively were noted by the recovery staff.

The patients were assessed by an experienced anaesthetist and deemed fit for discharge if they were free from significant pain, sedation and nausea, had no surgical complications such as continued blood loss, and could dress themselves and walk steadily. A direct enquiry about postoperative nausea and vomiting was made at this time, and questionnaires and prepaid envelopes were given to the patients with instructions that these should be completed 24 hours after discharge.

Statistical analysis. A one-way analysis of variance was used for parametric data and the Chi-squared test for nonparametric data.

Results

The results of six patients were excluded from the trial due to noncompliance with the protocol. The characteristics of the three groups were similar. There were no significant differences in age, weight or gestation. Significantly fewer patients in the group that received droperidol 0.5 mg had had a previous anaesthetic, and a significantly greater proportion of patients in both droperidol groups gave a history of nausea and vomiting after general anaesthesia. There was no significant difference in the time from administration of the prostaglandin to induction of anaesthesia, operating time and recovery time in the three groups (Table 1).

The incidence of pre-operative nausea (49% overall) and vomiting (29% overall) was high and was similar in all the groups. There was no significant difference in pre- and postoperative vomiting in the placebo group. Postoperative nausea was significantly decreased in both droperidol groups, but vomiting was significantly decreased only in the group that received 0.25 mg ($p < 0.05$, Table 2). There was no significant difference in nausea and vomiting postoperatively between those who received droperidol 0.25 mg and those who received droperidol 0.5 mg.

There was no significant difference in the postoperative administration of antiemetics or analgesics. The number of patients with nausea and vomiting, both before and after operation, was significantly reduced in both droperidol groups ($p < 0.05$, Table 3).

No patient required to be admitted overnight for anaesthetic or surgical complications. There was a 76% response to the questionnaire (Table 4). There was no significant difference in reported side effects experienced after discharge or in the patients' preference for day surgery.

Discussion

Prostaglandins are increasingly being used to facilitate vaginal termination of pregnancy. Their use in pessary form pre-operatively has been shown to reduce the force required for cervical dilatation and so, by implication, the risk of future cervical incompetence.[2–4] Intra-operative blood loss has also been shown to be reduced.[1,2] Nausea as a side effect, has generally been unrecorded; the incidence of vomiting was 15% in the study by McKenzie and Fry,[2] and 20% in that by Craft *et al.*[3] The relationship of vomiting to general anaesthesia was not given. The high incidence of nausea and vomit-

Table 1. Comparison of groups.

	Placebo	Droperidol 0.25 mg	Droperidol 0.5 mg
Number of patients	49	48	47
Mean (SD) age, years	24 (0.9)	23 (0.8)	25 (1.0)
Mean (SD) weight, kg	60 (1.3)	61 (1.1)	58 (1.9)
Mean (SD) gestation, weeks	9 (0.2)	10 (0.3)	10 (0.3)
Previous general anaesthetic (GA)	38 (78%)	36 (75%)	22 (47%)*
Nausea after previous GA	11 (29%)	17 (47%)*	14 (64%)*
Vomiting after previous GA	9 (24%)	16 (44%)*	11 (50%)*
Interval prostaglandin–GA, minutes	145 (5.9)	145 (5.2)	142 (6.5)
Duration of anaesthesia, minutes	8 (1.1)	8 (0.5)	8 (0.4)
Time to eye opening, minutes	7 (1.0)	8 (0.4)	8 (0.4)
Time to giving date of birth, minutes	9 (1.3)	10 (0.6)	10 (0.6)

* $p < 0.05$ compared with placebo group.

Table 2. Incidence of nausea and vomiting.

	Placebo (n = 49)	Droperidol 0.25 mg (n = 48)	Droperidol 0.5 mg (n = 47)
Pre-operative			
Nausea	24 (49%)	23 (48%)	23 (49%)
Vomiting	15 (31%)	13 (27%)	14 (30%)
Postoperative			
Nausea	20 (41%)	10 (21%)*	9 (19%)*
Vomiting	12 (25%)	5 (10%)*	8 (17%)
Postoperative drugs			
Antiemetics (metoclopramide)	5 (10%)	4 (8%)	4 (8%)
Analgesics (paracetamol)	17 (35%)	10 (23%)	10 (21%)

* $p < 0.05$ compared with placebo group.

Table 3. Individual patients' experience of nausea and vomiting.

	Placebo (n = 49)	Droperidol 0.25 mg (n = 48)	Droperidol 0.5 mg (n = 47)
Nausea			
Pre- and postoperative	15 (30%)	6 (13%)*	5 (11%)*
Pre-operative only	9 (18%)	17 (35%)*	18 (38%)*
Postoperative only	5 (10%)	3 (6%)	4 (9%)
Vomiting			
Pre- and postoperative	8 (16%)	2 (4%)*	4 (9%)*
Pre-operative only	8 (16%)	11 (23%)*	10 (21%)*
Postoperative only	2 (4%)	2 (4%)	4 (9%)

* $p < 0.05$ compared with placebo group.

ing is only too apparent to those who provide an anaesthetic service for patients who have received prostaglandins. In this study, 49% of patients were nauseated and 29% vomited pre-operatively. This incidence was largely unchanged postoperatively in the placebo group (41 and 25%), which demonstrates that general anaesthesia *per se* contributed little extra.

As a group, women who present for day case termination of pregnancy are especially prone to nausea and vomiting: they are young, anxious, pregnant and are having a gynae-

Table 4. Other side effects reported by patients by questionnaire.

	Placebo	Droperidol 0.25 mg	Droperidol 0.5 mg
Questionnaire returned	38 (78%)	34 (71%)	38 (81%)
Drowsiness	13 (34%)	12 (35%)	10 (26%)
Dizziness	8 (21%)	7 (21%)	6 (16%)
Nausea	1 (3%)	4 (12%)	3 (8%)
Vomiting	–	–	–
Heachache	10 (26%)	10 (29%)	9 (24%)
Abdominal pain	3 (8%)	7 (21%)	5 (13%)

cological operation with cervical dilatation. These are all factors which have been shown to be associated with increased postoperative emesis.[8–11] Patients with a history of nausea and vomiting after general anaesthesia are more likely to experience this after subsequent anaesthetics.[8] In our study, significantly more of the patients in the droperidol groups gave a history of postoperative nausea and vomiting, so the significant reduction of postoperative nausea which resulted might, if anything, be considered to be more meaningful.

It is our routine practice to prescribe metoclopramide 10 mg and ranitidine 150 mg preoperatively on arrival at the day surgery unit to reduce gastric volume[12,13] and increase gastric pH.[12–15] Several studies have failed to demonstrate any significant antiemetic effect after prophylactic metoclopramide,[16–18] but it has been reported to reduce postoperative emesis in patients who undergo gynaecological surgery.[19–21] Therefore, in order to assess the antiemetic effects of low dose droperidol, preoperative metoclopramide and ranitidine were omitted in patients in the study.

The general anaesthetic used is one which we have found suitable for day case termination of pregnancy. The combination of methohexitone and alfentanil provides good operating conditions swiftly and affords rapid recovery.[22–24] A decreased incidence of nausea and vomiting has been found after alfentanil compared with fentanyl,[23] but this has not been confirmed by others.[22] The addition of low concentrations of enflurane has been found to improve the quality of anaesthesia with alfentanil and etomidate[25] and we have found the same with alfentanil and methohexitone.

The efficacy of droperidol as a prophylactic antiemetic is well established, both as premedication[26–28] and given intravenously peroperatively.[5,29–31] However, when given as premedication without other sedative drugs it has been found to increase anxiety[28] and so is obviously not suitable for day case termination of pregnancy. In doses of 1.0–2.5 mg intravenously peroperatively it increases recovery time.[5] Valanne and Korttila[32] found that droperidol 1 mg slowed perceptual speed and recovery of walking ability, and larger doses have been shown to increase sedation.[31] Despite this it has been found compatible with same day discharge, but most anaesthetists would prefer not to give optional prophylactic drugs which might adversely affect postoperative recovery.

Shelley and Brown[33] reasoned that as chlorpromazine 25 mg is effective as an antiemetic, and as the antiemetic efficacy of droperidol is 100 times as great as that of chlorpromazine, ultra low dose droperidol 0.25 mg ought to be sufficient. This has been confirmed in several studies[5,6,33] but was not corroborated by Cohen *et al.*[34] Our study has shown low dose droperidol to reduce postoperative nausea significantly, from 41% in the placebo group to 21% after 0.25 mg and 19% after 0.5 mg; vomiting was reduced significantly after 0.25 mg and reduced, but not significantly, after 0.5 mg. This confirms O'Donovan and Shaw's[5] findings that 0.25 mg was as effective as 1.25 mg while it provided faster recovery. The 49% reduction of postoperative nausea and vomiting in our study compares favourably with the 50% reduction found by Madej and Simpson[35] after a dose of 2.5 mg.

The use of prostaglandin pessaries to facilitate vaginal termination of pregnancy was found to be associated with an unacceptably high incidence of nausea and vomiting. Droperidol 0.25 mg intravenously at induction of anaesthesia was found to decrease this significantly. No additional benefit was shown with droperidol

0.5 mg. Immediate recovery and postoperative side effects were not significantly different from the placebo group. It is concluded that prophylactic droperidol 0.25 mg at induction may enhance the quality of recovery in day case anaesthesia by reduction in nausea and vomiting, without adverse side effects.

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Failure of critically ill patients to metabolise midazolam

M. P. SHELLY, L. MENDEL AND G. R. PARK

Summary

The pharmacokinetics of midazolam and its metabolite, 1-OH midazolam, were studied in six critically ill patients during and after a continuous intravenous infusion of midazolam. Four patients had an increased elimination half-life of midazolam; two were associated with a reduction in plasma clearance with low plasma concentrations of the metabolite, and two with normal metabolite levels and increased volume of distribution. The two patients with reduced clearance suffered from septic shock and were studied over a longer period. Their altered clearance was due to a reduced capability to form the 1-OH metabolite. As their condition improved, plasma concentrations of 1-OH midazolam increased and midazolam clearance returned towards normal. The impaired ability of critically ill patients with septic shock to metabolise midazolam, may be due to reduced organ perfusion and may lead to cumulation of midazolam in these patients.

Key words

Hypnotics, benzodiazepines; midazolam.
Pharmacokinetics.

Sedation of patients who require intensive care is necessary to reduce the distress of the patient and to facilitate treatment. Several agents are available but all have disadvantages when given continuously to critically ill patients. Accumulation of barbiturates may lead to prolonged sedation after the infusion has been discontinued. Chlormethiazole has been used[1] but the large fluid volume required may compromise fluid balance and nutrition. Etomidate and alphaxalone/alphadalone (Althesin) provide effective sedation when given by continuous infusion, but problems with their use have led to their being abandoned.[2–4]

Until the introduction of midazolam, benzodiazepines have not been used by continuous intravenous infusion because of the prolonged effect of the parent drug and, in some cases, of its pharmacologically active metabolites. Midazolam is a water soluble benzodiazepine with a rapid onset and a short duration of action in normal subjects.[5] It has a short elimination half-life, a relatively large volume of distribution and a high plasma clearance.[6] Its major metabolic pathway is hydroxylation and subsequent conjugation with glucuronic acid before elimination in the urine. Midazolam is thought to undergo biotransformation by the P450 system[7]

M.P. Shelly,* FFARCS, Research Registrar, L. Mendel, FFARACS, Research Fellow, G.R. Park, FFARCS, Consultant in Anaesthesia and Intensive Care, Department of Anaesthesia, Addenbrooke's Hospital, Cambridge.
* Present position: Senior Registrar, Odstock Hospital, Salisbury, Wilts.
Correspondence should be addressed to Dr G.R. Park please.

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and, since it undergoes extensive first pass metabolism following oral administration, the liver and gut wall are thought to be important sites of metabolism although other organs may also be involved. The 1-hydroxy metabolite of midazolam is pharmacologically active but has a shorter elimination half-life than midazolam itself.[8]

A prospective study was performed to investigate the pharmacokinetics of midazolam in critically ill patients. Prolonged sedation following continuous intravenous infusion of midazolam was reported[9–11] while this study was being planned, and the blood sampling protocol was extended in view of this.

Method

Six consecutive critically ill patients who had not received benzodiazepines since admission to the intensive care unit and who required sedation to facilitate controlled ventilation, received a continuous intravenous infusion of midazolam. Approval for the study was obtained from the district ethics committee. Informed consent was obtained from three of the patients themselves (patients C, D and E) but the remainder were unable to consent personally and informed consent for the study was then obtained from their relatives.

Midazolam hydrochloride was diluted with 5% dextrose to produce a solution that contained 1 mg/ml and administered through a centrally placed venous catheter. The rate of infusion was altered by the nursing staff subject to prescribed limits which were reviewed regularly by medical staff. No other benzodiazepines were administered during the study period.

Blood samples were withdrawn from an indwelling arterial line into tubes that contained oxalate anticoagulant, before the infusion was commenced and one hour after starting the infusion; thereafter daily blood samples were taken to ascertain whether steady state had been reached. Frequent blood samples were taken following cessation of the infusion, until the patient was clinically awake (Table 1). The blood was centrifuged and the supernatant plasma separated and stored at −20°C for analysis. Plasma concentrations of midazolam and the metabolite 1-OH midazolam were estimated by gas–liquid chromatography with electron capture detection.[12]

Table 1. Times of blood sampling during continuous intravenous infusion of midazolam.

Before administration of midazolam
One hour after commencement of infusion
Daily sampling at 10:00 hours
On cessation of infusion
Thereafter at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 hours
Six-hourly until the patient wakes

Pharmacokinetic parameters for midazolam were determined using standard, model-independent pharmacokinetic methods. It was assumed that a steady state would be reached if midazolam was infused continuously at the same rate for 15 hours or more.

The severity of the patients' illness was assessed by determination of their APACHE II score[13] on admission to the intensive care unit and on the day of cessation of the midazolam infusion. The sepsis score[14] was also calculated for each patient on admission and daily thereafter. Note was made of all other drugs administered to the patients, particularly other sedative and analgesic drugs and inotropic agents.

Throughout their period of intensive care, the conscious level of each patient was recorded every 2 hours using a sedation scoring system developed for routine use in this intensive care unit.[15] This system uses six clinically identifiable end points; fully alert, roused by voice, roused by pain, unrousable, paralysed, or asleep. The time taken for the patients to wake following cessation of the midazolam infusion was noted from the recorded conscious levels and taken as the point where the patient became fully alert or increased their conscious level by at least two steps. The plasma concentrations of midazolam and of the metabolite 1-OH midazolam at the point of awakening were extrapolated from the graphs of plasma drug and metabolite concentrations against time.

Results

The details of the six patients are shown in Table 2. One patient failed to complete the protocol and a further patient was studied on two occasions. Patient E received an infusion of midazolam for 16 days to facilitate controlled ventilation. No samples were taken during the decline phase after cessation of the infusion but his results are included because of the duration of the infusion. In patient F, the infusion was discontinued on

Table 2. Details of the six patients studied.

Patient	Age (years)	Sex	Weight (kg)	APACHE II score*	Sepsis score*	Diagnosis
A	76	M	78	a 14	2	Prolonged postoperative neuromuscular
				b 14	2	blockade
B	68	M	66	a 20	6	Postcardiac arrest
				b 17	5	
C	54	F	60	a 8	0	Multiple trauma
				b 3	3	
D	62	M	70	a 16	12	Re-exploration of femoro-popliteal graft
				b 17	10	
E	60	M	60	a 30	20	Chronic myeloid leukaemia, septic shock
				b 32	18	
				c 26	13	
F	76	M	60	a 26	13	Postoperative respiratory failure, septic
				b 29	19	shock
				c 24	17	

* a, On admission; b, on day of cessation of midazolam infusion, except for patient E, day 4 scores; c, patient E, scores on day 14, patient F, scores on the second occasion when the midazolam infusion was stopped.

Table 3. The mean dose of midazolam, the duration of infusion and other sedative, analgesic and vasoactive drugs administered to each patient.

Patient	Mean dose (mg/hour)	Infusion duration (hours)	Analgesics	Vasoactive agents
A	2.7	10	Morphine	
B	6.4	26	Morphine	Dopamine
				Lignocaine
				Digoxin
C	3.4	143	Morphine	Dopamine
D	3.8	39	Morphine	Dopamine
E	7.0	369	Morphine	Dopamine
			Alfentanil	Dobutamine
			Fentanyl	Methoxamine
				Phenylephrine
				Digoxin
				Adrenaline
				Verapamil
F	4.6	159	Morphine	Dopamine
			Alfentanil	Dobutamine
				Methoxamine
				Adrenaline
				Digoxin

the 5th day to assess the patient's conscious level but was restarted to control agitation. The infusion was finally stopped 3 days later to attempt weaning from controlled ventilation. Blood samples were taken on each occasion the infusion was stopped. All the patients except patients E and F survived to be discharged to the ward. Patient E died on his 20th day of intensive care, 5 days after his last dose of midazolam and patient F died on his 82nd day of intensive care, 75 days after his infusion ended; both died of multisystem failure. APACHE II and sepsis scores are shown for patient E on day 4 of his midazolam infusion, when he suffered from septic shock, and on day 14, when clinical improvement was evident. The same scores are shown for patient F on both days his sedation was discontinued.

In all the patients, the infusion of midazolam was commenced shortly after their admission to the intensive care unit. The dose and duration of the infusions are shown in Table 3, together with other sedative, analgesic and vasoactive agents administered. None of the patients received other benzodiazepines or neuromuscular blocking agents during the study period. Concomitant drugs administered included antibiotics, steroids, heparin and diuretics. All patients

received ranitidine and morphine, which was administered by intravenous bolus dosage or by continuous intravenous infusion. Dopamine was given by continuous intravenous infusion to all but patient A. Patients A and C had normal renal function, patients B and D had impaired renal function whilst patients E and F were in renal failure. Only patients E and F had impaired liver function and reduced serum albumin concentrations.

The derived pharmacokinetic parameters are shown in Table 4, together with the normal values.[16,17] One patient (C) had normal pharmacokinetic parameters and in another (A), the data were incomplete but appeared normal. The remaining patients had prolonged elimination half-lives as a result of reduced clearance of midazolam. In two cases (patients B and D), plasma concentrations of 1-OH midazolam were normal and the increased half-life was due partly to an increased volume of distribution.

Two patients (E and F) initially had a reduced clearance of midazolam with increasing plasma concentration of midazolam during the period of their infusion and low or absent plasma concentrations of 1-OH midazolam. As their condition improved, plasma concentrations of midazolam

Table 4. Pharmacokinetic parameters for midazolam in each patient.

Patient	Clearance (litres/kg/hour)	Half-life (hours)	Volume of distribution (litres/kg)
Normal range[16,17]	0.24–0.71	0.84–5.4	0.86–1.86
A	*	2.5	*
B	0.11	13.9	2.23
C	0.42	2.5	1.51
D	0.06	18	High †
E a	0.04	*	*
b	0.49		
F a	0.03	21	0.88
b	0.08	7.8	0.98

* No values: patient A, not at steady state when infusion discontinued; patient E, no samples during decay from plateau level.

† Clearance at steady state probably reduced due to interfering peak in predose sample.

a, Patient E, day 4, patient F, first cessation of midazolam infusion; b, patient E, day 14, patient F, second cessation of midazolam infusion.

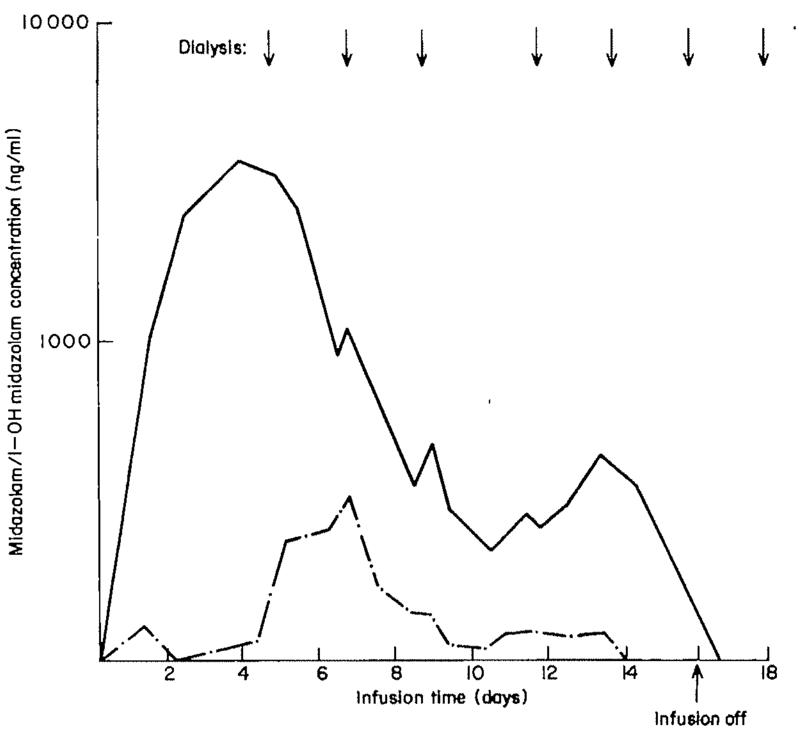

Fig. 1. Plasma midazolam and 1-OH midazolam concentrations for patient E throughout the period of study. ——, Plasma midazolam concentration; –·–·–, plasma 1-OH midazolam concentration.

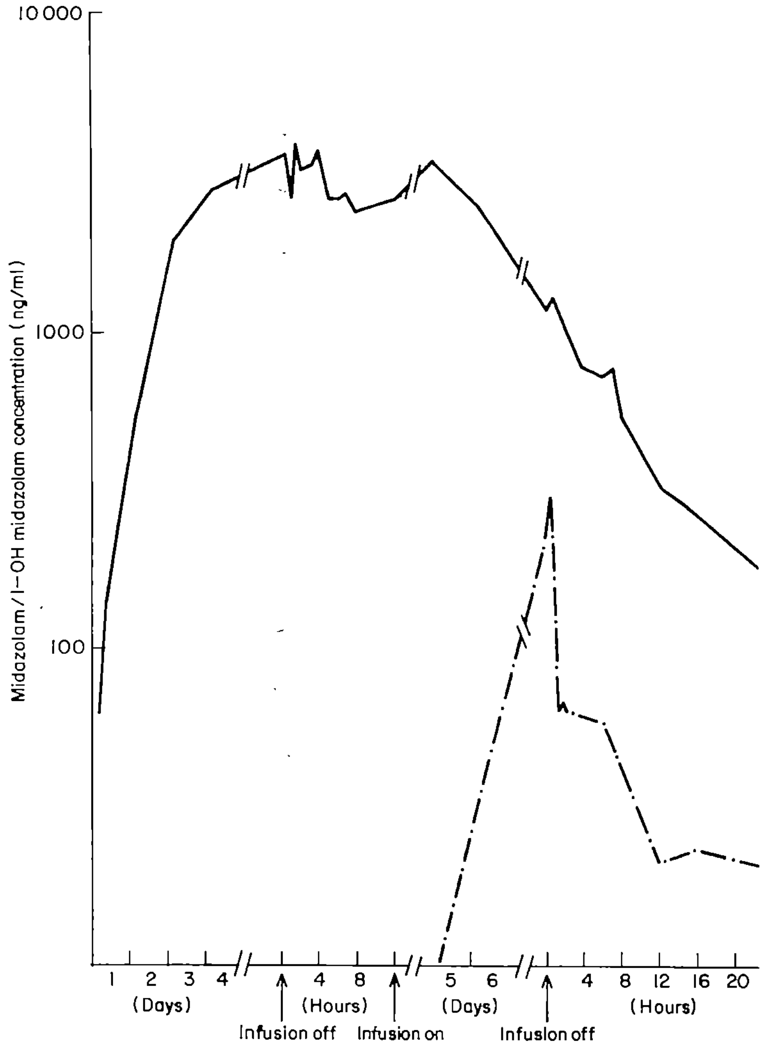

Fig. 2. Plasma midazolam and 1-OH midazolam concentrations for patient F during the study period, including both occasions the midazolam infusion was discontinued. ——, Plasma midazolam concentration; –·–·–, plasma 1-OH midazolam concentration.

decreased and 1-OH midazolam increased, which indicates that clearance was returning towards normal. The plasma concentrations of midazolam and 1-OH midazolam for patient E throughout the period of his infusion are shown in Fig. 1. Plasma concentrations of midazolam increased rapidly after the start of the infusion and reached a peak on day 4. Plasma concentrations of 1-OH midazolam were low or absent during this time. On day 5, which coincided with the patient's first period of haemodialysis, the plasma concentration of midazolam decreased but that of 1-OH midazolam increased. Following this, the plasma concentrations of midazolam and 1-OH midazolam decreased to a steady-state level which was maintained until the infusion was discontinued. The phase immediately following discontinuation was not studied in this patient but, 24 hours after cessation of the infusion, no midazolam or 1-OH midazolam were detectable in the plasma.

The plasma concentrations of midazolam and 1-OH midazolam for patient F during his entire study period are shown in Fig. 2. Plasma con-

centrations of midazolam again increased rapidly to high levels by day 4 but, following the first cessation of the infusion, the levels remained high. No 1-OH midazolam was detected in the plasma during this period. After the infusion was restarted plasma midazolam concentrations declined slightly until the infusion was finally stopped on day 8. Following this, the plasma concentration decreased to therapeutic levels within 24 hours.

Table 5 shows the time taken for the patients to wake and the plasma concentrations of midazolam and 1-OH midazolam at this time.

Table 5. Time taken for patients to wake following cessation of midazolam infusion, and plasma midazolam and 1-OH midazolam concentrations at this time.

Patient	Time to wake (hours)	Plasma midazolam concentration (ng/ml)	Plasma 1-OH midazolam concentration (ng/ml)
A	0	117	25
B	11	365	43
C	2	97	40
D	12	519	32
E	*	0	0
F a	†	2582	0
b	24	166	20

* Remained unrousable.
† Infusion restarted because of agitation.
a, First cessation, b, second cessation of midazolam infusion.

Discussion

Few drugs are currently available which will predictably produce adequate sedation in patients who receive intensive care. Midazolam has been used to induce anaesthesia[18] and to produce sedation[19] in healthy patients and its use has been extended to the critically ill patient in the intensive care unit. Continuous intravenous infusion of midazolam produces satisfactory sedation but prolonged awakening has been reported in some patients.[9–11] A considerable variation in individual response to midazolam has been reported previously; the elderly are particularly sensitive.[20] The prolonged sedation seen in critically ill patients following midazolam may represent part of a spectrum of response and may reflect altered hepatic blood flow[9] or impaired metabolic capacity.[20] The patients reported here show three different pharmacokinetic and pharmacodynamic patterns, which appear to be related to the severity of the patient's disease.

The two patients (A and C) with the lowest APACHE II and sepsis scores had normal pharmacokinetic parameters. In both these patients, plasma concentrations of midazolam and 1-OH midazolam decreased rapidly and both woke soon after the infusion was discontinued. At the time of awakening, plasma concentrations of midazolam were approximately 100 ng/ml and concentrations of 1-OH midazolam were approximately 30 ng/ml.

All the remaining patients had a low plasma clearance and a prolonged elimination half-life of midazolam. Two of these patients (B and D) had intermediate APACHE II and sepsis scores. The prolonged elimination of midazolam in these patients, was associated with a large volume of distribution and normal plasma concentrations of 1-OH midazolam. These patients remained sedated for approximately 12 hours after cessation of the infusion and were awake, with plasma concentrations of midazolam normally associated with sedation. Plasma concentrations of 1-OH midazolam were again approximately 30 ng/ml. Patients who undergo major surgery and patients with chronic renal failure have an altered volume of distribution of midazolam.[20,21] This change has been attributed to reduced protein binding of the drug, which leads to a higher free drug fraction.[21] A similar mechanism may be responsible for the large volume of distribution of midazolam in these patients, both of whom had impaired renal function. Their concentrations of serum albumin were normal but its ability to bind midazolam may have been altered by disease or other drugs administered concomitantly.[22]

The remaining two patients (E and F) both initially suffered from septic shock and had high APACHE II and sepsis scores; both patients received inotropic support. These two patients initially had a reduced clearance associated with low or absent plasma concentrations of 1-OH midazolam. The plasma concentration of midazolam in these patients reached high levels (3000 ng/ml) on the 4th and 5th day of their infusions but no adverse haemodynamic or biochemical effects of these high concentrations were noted. Both patients subsequently showed clinical evidence of improvement and their APACHE II and sepsis scores decreased. This improvement was associated with the appearance

of 1-OH midazolam in their plasma and an increase in midazolam clearance towards normal. In patient E, this change coincided with his first period of haemodialysis. This did not initiate his improvement but is a reflection of it, since haemodialysis could not be undertaken in the presence of haemodynamic instability. Furthermore, similar changes in the plasma concentrations of midazolam and 1-OH midazolam were not seen when haemodialysis was repeated.

The high plasma concentrations of midazolam and the absence of metabolite suggest that impaired metabolism resulted in its cumulation. A reduction in the metabolism may result from reduced liver perfusion or an enzyme defect.[23] The increase in midazolam clearance as the patients' condition improved, however, suggests a reversible impairment rather than an inherited reduction in midazolam metabolism.[20] Because midazolam has a high hepatic extraction, the rate of its metabolism is dependent on hepatic blood flow and any reduction in liver perfusion could reduce the rate of its metabolism.[9] Acute hypovolaemia in dogs lowered the clearance of midazolam, without changes in volume of distribution or in protein binding.[24] Midazolam itself has been shown to affect splanchnic blood flow. Following bolus administration, hepatic arterial flow decreases and portal venous flow, after an initial rise, also falls.[25] The haemodynamic stability that follows administration of midazolam is thought to be due to compensatory mechanisms which lead to redistribution of blood within the splanchnic bed; this may also occur in man.[26]

Both these patients were sedated for a prolonged period following cessation of the infusion. Patient E remained unrousable until his death, in spite of undetectable plasma concentrations of midazolam and 1-OH midazolam 22 hours following the infusion; this may have been due to the prolonged effect of other drugs or to his severe illness. After the midazolam infusion of patient F had been discontinued, it was restarted because of agitation which occurred in spite of a high plasma concentration. However, when the infusion was discontinued for a second time, he woke with a plasma concentration of midazolam within the sedative range and a plasma 1-OH midazolam concentration of 20 ng/ml. Overall, there appeared to be no correlation between plasma midazolam concentration and the time at which the patient woke following the infusion. There does, however, appear to be an association between waking and the plasma concentration of 1-OH midazolam; patients awoke with levels between 20 and 40 ng/ml.

Plasma concentrations of 1-OH midazolam are lower than those of the parent drug and this represents a wide range. However, it may be that the action of midazolam is influenced by its metabolites in the same way as the effects of morphine appear to depend upon its metabolites.[27,28]

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CASE REPORT

Somatostatin, anaesthesia, and the carcinoid syndrome

Peri-operative administration of a somatostatin analogue to suppress carcinoid tumour activity

R. C. ROY, R. F. CARTER AND P. D. WRIGHT

Summary

A patient with carcinoid syndrome on long-term antiserotonin therapy with parachlorophenylalanine, experienced a flushing attack with hypotension during the prophylactic administration of aprotonin prior to the induction of anaesthesia. When she was subsequently prepared with a long-acting somatostatin analogue, octreotide (Sandostatin, Sandoz SMS 201–995), plasma levels of tumour-released hormones were reduced and anaesthesia for resection of hepatic metastases was uneventful. The advantages of an anaesthetic approach based on inhibition of carcinoid tumour activity, rather than antagonism of released hormones, are discussed.

Key words

Complications; carcinoid tumour.
Hormones; somatostatin, serotonin.

Serotonin and bradykinin are no longer accepted as the only, or even primary, mediators of the carcinoid syndrome.[1–4] Carcinoid tumours are now known to synthesise more than twenty substances which influence vascular, bronchial and gastrointestinal smooth muscle activity.[1] There is no clear association between these messengers and symptoms[2] so that an anaesthetic technique based on antagonism of released mediators is still a theoretical concept.

Carcinoid tumours retain their responsiveness to physiological and pharmacological effectors of enterochromaffin cell activity.[2] Somatostatin and its newly synthesised longer-acting analogues[5,6] prevent the release of active mediators from carcinoid tumours.[2,7–10] Thus, an anaesthetic approach based on global inhibition of tumour activity and avoidance of triggering agents and situations, is now possible.

This report describes a patient on long-term antiserotonin therapy in whom a carcinoid crisis occurred during treatment with additional antiserotonin and antibradykinin agents prior to the induction of anaesthesia. When she was treated subsequently with a long-acting somatostatin analogue, octreotide (Sandostatin, Sandoz SMS 201–995), plasma levels of tumour-released mediators fell. She then underwent an uneventful anaesthetic for resection of hepatic metastases. This is the first report to describe a patient with carcinoid syndrome given a somatostatin analogue prophylactically in preparation for anaesthesia.

R.C. Roy,* PhD, MD, Visiting Lecturer, Honorary Consultant, Department of Anaesthetics, University of Newcastle-upon-Tyne, R.F. Carter, FFARCS, Consultant, P.D. Wright, MD, FRCS, Consultant Surgeon, Freeman Hospital, Newcastle-upon-Tyne NE7 7DN.

*Present address: Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, Winston–Salem, North Carolina 27103, USA.

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Case history

A 46-year-old, 54-kg female with carcinoid syndrome presented for resection of hepatic metastases. The diagnosis was based on a long history of diarrhoea and flushing and the finding of elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) concentrations. The primary tumour, presumed pre-operatively to be in the pancreas because of grossly elevated plasma levels of pancreatic polypeptide (PP),[11] was determined at surgery to be unresectable.

Initially her diarrhoea was episodic and appeared to increase during times of stress. When frequency increased despite loperamide, methysergide was prescribed. It was discontinued because of intolerable side effects: facial paraesthesiae, twitching of arms and legs, and hallucinations. Parachlorophenylalanine (PCPA) reduced stool frequency and lowered urinary 5-HIAA levels. Fatigue was possibly the only side effect of PCPA observed; there was no light-headedness, tinnitus, headache, dyspnoea, urticaria, eosinophilia or pulmonary infiltration.[12] The initial dose of PCPA, 500 mg orally every 8 hours, was increased to 1 g orally twice daily.

The tumour also secreted large amounts of gastrin. Endoscopy revealed multiple ulcerations in her stomach and duodenum. Ranitidine, 150 mg orally twice daily, was prescribed to oppose the stimulating effect of gastrin on acid secretion from parietal cells. Plasma levels of other peptide hormones—ACTH, growth hormone, calcitonin, insulin, vaso-active intestinal peptide, glucagon and neurotensin—were within normal limits.

Endoscopy also revealed oesophageal varices, the aetiology of which was established to be portal vein thrombosis, diagnosed during the venous phase of mesenteric arteriograms. She also had splenomegaly. During the period of preparation for surgery the patient experienced one upper gastrointestinal bleeding episode which was controlled by application of a Sengstaken–Blakemore tube. She was also given aprotonin (Trasylol) at this time, with no untoward reaction. Her varices were injected with ethanolamine oleate four times under general anaesthesia prior to her liver surgery. The first anaesthetic consisted of thiopentone, suxamethonium, fentanyl, isoflurane, nitrous oxide (rapid sequence induction–intubation), and the subsequent three of alfentanil, etomidate, vecuronium, isoflurane and nitrous oxide. All four anaesthetics were uneventful.

On the morning of her scheduled surgery, she arrived in the anaesthetic room anxious, although she had received diazepam 10 mg one hour earlier. Her arterial pressure was 140/90 mmHg and heart rate 98 beats/minute. Droperidol 2.5 mg and chlorpromazine 2.5 mg were given intravenously and, 5 minutes later, an aprotonin infusion was started as prophylaxis for reactions that involve bradykinin. Within one minute the patient's head and upper body turned a fiery red colour and she complained of dyspnoea and chest tightness. Auscultation revealed high volume breath sounds without wheezing. She later stated that she felt that she was going to die. Her arterial pressure initially increased to 170/102 mmHg and then decreased to values within the range 85–100/37–77 mmHg. Her heart rate initially increased to 164 beats/minute, then settled between 115 and 150; the ECG showed sinus tachycardia. Oxygen and intravenous fentanyl 50 μg and midazolam 1.25 mg calmed her but did not alter her cardiovascular status. One hour later an additional dose of midazolam 1.25 mg was given and ketanserin 4 mg administered intravenously, with no haemodynamic changes. Her symptoms abated gradually over the next 2 hours. Surgery was cancelled.

Treatment with a somatostatin analogue, octreotide (Sandostatin, Sandoz SMS 201–995), was started at a dose of 100 μg subcutaneously twice daily. Her diarrhoea stopped during the first day of therapy. Her dosing regimen was changed to 100 μg subcutaneously every 8 hours because she sensed an increase in gastrointestinal activity 45 minutes prior to each scheduled octreotide injection. PCPA and ranitidine were continued. Ten days after the octreotide injections were initiated, her plasma levels of PP and gastrin were much lower and urinary levels of 5-HIAA were within normal limits (Table 1).

When she presented for surgery again after 2 weeks of octreotide therapy, she was less anxious than on the previous occasion, despite the same premedication, diazepam 10 mg, given 1 hour earlier. Ranitidine 50 mg and octreotide 100 μg were administered intravenously immediately prior to induction of anaesthesia. Fentanyl 250 μg was given in divided doses followed by etomidate 10 mg, vecuronium 6 mg and isoflur-

Table 1. Response of abnormal hormone levels to pharmacological treatment and surgery.

	Months				
	1	3	5	6	
				Pre-operative	Postoperative
Hormones					
PP*	616	>1000	>1000	236	56
Gastrin†	288	950	>400	346	34
5-HIAA‡	187	54	86	19	—
Treatment					
PCPA§	−	+	+	+	−
Octreotide	−	−	−	+	+

* Pancreatic polypeptide, normal <300 pmol/litre plasma.
† Normal <40 pmol/litre plasma.
‡ 5-Hydroxyindoleacetic acid, normal <40 μmol/litre urine, average over 3 days.
§ Parachlorophenylalanine.

ane. These agents were chosen on the basis of their low capacity to release histamine. Nitrous oxide 70% was added after tracheal intubation. Her initial arterial pressure and heart rate were 132/72 mmHg and 80 beats/minute. Her arterial pressure decreased to 103/62 mmHg on induction, increased to 124/81 mmHg with intubation, decreased to 103/51 mmHg prior to incision and increased to 146/107 mmHg with incision. Heart rate was 68–72 beats/minute before incision and 86–106 intra-operatively. Systolic arterial pressure was maintained easily between 100 and 140 mmHg by volume administration and adjustment of the inspired isoflurane concentration. A left radial arterial cannula and right external jugular central venous pressure catheter were inserted following induction of anaesthesia.

Splenectomy, gastric devascularisation, inspection of the pancreas, left hepatic lobectomy and excision of two reasonably well-encapsulated metastases were performed. The estimated blood loss was 3725 ml. The patient received six units of blood, 1500 ml of hetastarch and 1200 ml of 5% glucose. All fluids were warmed and the blood filtered through a 40-μm filter. Inspired gases were warmed and humidified, and a warming blanket used, but the nasopharyngeal temperature decreased from 35.8 to 34.3°C. The end tidal carbon dioxide concentration was maintained between 4.7 and 5.1% by adjustment of the ventilation. Because of the low temperature and concern about postoperative bleeding, she was transferred to the intensive therapy unit where she was sedated, paralysed and her lungs ventilated artificially.

Her postoperative course was complicated by severe bleeding which required re-exploration and extensive administration of blood products. Additional intravenous octreotide 100 μg was given prophylactically. A bleeding site was found which could have accounted for the blood loss. An episode of supraventricular tachycardia, treated by cardioversion, occurred when she was hypotensive while bleeding. A macular rash that covered the upper half of her body was noted one hour after an octreotide injection, but it did not recur after subsequent injections of octreotide. Plasma glucose concentration varied from 8.4 to 20.8 mmol/litre intra-operatively, and postoperatively until day 3, but no insulin was given.

Octreotide dosage was tapered postoperatively as follows: 100 μg subcutaneously every 8 hours on postoperative days 1–3, every 12 hours on days 4–6 and once daily on days 7–9; treatment was then stopped. Plasma levels of PP and gastrin were normal on postoperative days 1 and 3. She was discharged home on postoperative day 14.

Discussion

When serotonin (5-hydroxytryptamine) and kallikrein–bradykinin were considered to be the two active mediators released by carcinoid tumours, serotonin was held responsible for hypertension, tachycardia, diarrhoea and valvular heart lesions, and bradykinin for hypotension, bronchoconstriction and flushing.[13,14] Demonstration of serotonin overproduction, as manifested by excessive urinary levels of 5-HIAA, still remains the *sine qua non* of the laboratory diagnosis, but more than twenty humoral messengers are now recognised as possible mediators for the

carcinoid syndrome.[1] For example, substance P, found in high concentrations in carcinoid tumours and in the plasma of patients with carcinoid syndrome,[3,4] is a potent stimulator of gastrointestinal activity and 100 times more potent than bradykinin as a vasodilator.[4,15] Substance P infusions in humans produce a flush over the head and neck, and lower arterial pressure and heart rate.[15] Elevated plasma serotonin, gastrin and pancreatic polypeptide levels were documented in this patient, but substance P, histamine and kallikrein levels were not determined.

The failure of aprotonin to prevent hypotension and flushing in this patient, matches the experience of others who were unable to stop spontaneous or catecholamine-provoked flushing with aprotonin in patients with carcinoid tumours.[14] Either aprotonin is a weak inhibitor of kallikrein, which releases bradykinin from kininogen, or bradykinin is not the primary mediator of flushing and hypotension. Thus, despite enthusiasm for its use,[13,16,17] current clinical experience tends to argue against the prophylactic use of aprotonin in these patients.[14,18,19] However, Dery[13] and Keens *et al.*[20] described the resolution of hypotensive crises with aprotonin.

In anaesthetised patients with carcinoid syndrome, flushing was associated with hypotension in those treated pre-operatively with non-specific serotonin antagonists, but no hypotension was observed in untreated patients.[18] In this patient, who was pretreated with chlorpromazine and droperidol, hypotension was also observed during the flushing attack. Thus, either the mediators for flushing and hypotension are not the same, or serotonin offsets the hypotensive effect of another mediator.

Evidence now suggests that serotonin is not the substance which causes flushing.[2,18] Vasodilator peptides of the tachykinin family (neuropeptide K, neurokinin A and substance P) are more likely candidates.[2] However, the observation that a combination of histamine H_1 and H_2 blockers stops flushing in patients with gastric carcinoid, suggests a role for histamine.[21] The ability of ketanserin, a selective serotonin-2 receptor antagonist, to prevent flushing[22] may be related to its antihistamine or its adrenergic blocking actions.[23]

The occurrence of flushing and hypotension soon after the start of the aprotonin infusion, suggests that aprotonin may have caused the attack. The patient did have a prior, uneventful exposure to aprotonin which could have sensitised her, but an anaphylactic reaction was considered less likely than a carcinoid one because the flush was characteristic of those described for patients with carcinoid syndrome[2,24] and because there was no urticaria, oedema, bronchospasm or cardiovascular collapse.

Hypertensive crises can also occur in patients with carcinoid syndrome. No correlation was observed between plasma serotonin concentrations, or changes in concentration, and the absolute level of, or changes in, either arterial pressure or heart rate.[18] Ketanserin resolved a hypertensive crisis in a carcinoid patient on cardiopulmonary bypass[25] and provided stable haemodynamics in an anaesthetised patient with a carcinoid tumour despite high plasma concentrations of serotonin,[26] but its antihypertensive effect may be more related to its alpha-1 adrenergic blocking action than to its antiserotonin effect.[27]

Thus, multiple messengers, unclear association between messengers and symptoms, and unclear mechanisms of action for purported antagonists, condemn the patient with carcinoid syndrome to a treatment regimen with multiple drugs which are only moderately effective and which have significant side effects. Even if the antagonists are effective, tumour release of active agents can exceed the capacity of antagonists present. This situation is especially likely during anaesthesia, because of surgical manipulation of the tumour and because of tumour responsiveness to physiological and pharmacological stimuli. Pharmacological agonists include adrenergic agonists, such as adrenaline and noradrenaline,[2] and may include drugs which trigger the release of histamine and serotonin, such as morphine and tubocurarine.[2,14] Physiological events which may enhance tumour activity include those which involve endogenous release of catecholamines, for example stress, hypotension, hypercapnia and hypothermia.[28] Anxiety-related stress may have contributed to the crisis in this patient.

Somatostatin, a naturally occurring tetradecapeptide,[7] brightens this gloomy picture because it potentially eliminates the need for antagonists by inhibiting the release of active mediators from carcinoid tumours.[2,8–10,29,30] Somatosta-

tin acutely alleviated hypotension and bronchospasm in anaesthetised patients but rebound hypotension and bronchospasm occurred on its withdrawal.[29,30] The rapid onset of action of somatostatin means that the duration of action of messengers released by carcinoid tumours is short, because somatostatin does not antagonise mediators after their release.[2,7,8] It would be of interest to know whether somatostatin can relieve hypertension associated with carcinoid tumour activity but the only reported anaesthetic experience has been in response to hypotensive crises.[29–31]

Somatostatin must be administered by continuous infusion because its half-life is 1.1–3.0 minutes.[32] More potent and longer-acting somatostatin analogues have recently been synthesised[5,6] with plasma disappearance half-times of 45 minutes after intravenous, and 80 minutes after subcutaneous administration.[33] Subcutaneous octreotide 100 μg suppressed pentagastrin-induced gastric acid secretion for 5 hours in normal patients.[33] In this patient, if uncomfortable gastrointestinal activity is used as an end point, octreotide 100 μg provided relief for 11 hours. The onset of action of intravenous octreotide is also rapid, because it quickly relieved a severe hypotensive crisis intra-operatively.[31]

The subcutaneous administration of octreotide over one year reduced urinary 5-HIAA levels and stopped diarrhoea and flushing in 22 of 25 patients.[8] In our patient, in whom PCPA was continued, octreotide resulted in normal urinary 5-HIAA levels and lower plasma concentrations of PP and gastrin.

In normal patients, the plasma concentration of somatostatin required to suppress release of a particular peptide hormone, varies with the peptide hormone. Low concentrations inhibit gastric acid secretion, higher levels block insulin and glucagon release, and still higher concentrations are required to prevent gastrin release.[34] The same seems to apply to the somatostatin analogues. The persistently high gastrin levels in our patient suggest that the tumour was not completely shut down. For this reason, additional octreotide was given intravenously prior to the induction of anaesthesia and more was available in the operating theatre in case of a carcinoid crisis.

A possible side effect of somatostatin may be glucose intolerance.[7] Plasma levels of glucose were elevated intra-operatively and during 3 days postoperatively, but it was not possible to say that these elevations were due primarily to octreotide.

In summary, the use of a somatostatin analogue to inhibit tumour activity appears to be a major breakthrough in the care of these patients in general, and in anaesthetic management in particular. The role of antagonists of serotonin, bradykinin and histamine, is now being reevaluated. Based on our experience with this patient and a review of the literature, we recommend the following approach to patients with carcinoid syndrome: inhibit tumour activity with a somatostatin analogue; maintain normovolaemia;[35] avoid physiological triggers of tumour activity by preserving normocapnia, normotension and normothermia; use anaesthetic agents and adjuvants which do not trigger the release of histamine; have drugs available intra-operatively to treat a carcinoid crisis, including a somatostatin analogue; and maintain vigilance well into the postoperative period.

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CASE REPORT

Hypertension during anaesthesia with monoamine oxidase inhibitors

C. A. SIDES

Summary

A hypertensive response to the induction of anaesthesia with etomidate and atracurium in a patient who recently received tranylcypromine is described. The possible cause is discussed.

Key words

Pharmacology; monoamine oxidase inhibitors.
Complications; hypertension.

The interaction of monoamine oxidase inhibitors (MAOIs) with various drugs and foodstuffs is well recognised, particularly with cheese, and is due to the indirect sympathomimetic action of tyramine found particularly in old cheese. The resultant stimulation leads to an outpouring of noradrenaline from sympathetic nerve endings where it has accumulated in large amounts due to the inhibition of its metabolism by monoamine oxidase. Anaesthesia often involves polypharmacy and we must be ever vigilant for interactions. Some of these may be helpful, such as the potentiation of neuromuscular blockade by volatile agents, whilst others, such as the interaction between verapamil and halothane, are not.

Because MAOIs may have adverse effects with many anaesthetic agents it has, until recently, been advised that these agents be discontinued prior to anaesthesia. However, this has not always been possible for emergency surgery. Recent work has questioned whether this need be so and suggests that these patients can be anaesthetised safely whilst their therapy is continued.

Case history

A 61-year-old female with a long psychiatric history of narcolepsy had taken dexamphetamine 12.5 mg daily for the past 3 years and intermittently for the previous 15 years. On this occasion she was admitted for withdrawal from the dexamphetamine because of nightmares. The drug was stopped and approximately 36 hours later she was started on tranylcypromine 10 mg twice daily, since MAOIs have the ability to suppress rapid eye movement sleep and are therefore useful in the treatment of narcolepsy.

Her artertial pressure on admission was recorded as 140/100 mmHg and on discharge as 170/90 mmHg. She was later admitted after 9 days, following a self-administered overdose of a benzodiazepine. Following this her tranylcypromine was increased to 20 mg twice daily. During this latest admission she complained of a lump in her neck; further examination revealed extensive carcinoma of the breast and she was scheduled for a mastectomy. In view of her recent MAOI ingestion over the previous 2 months, balanced against her need for definitive

C.A. Sides, MB, ChB, FFARCS, Senior Registrar, St James's University Hospital, Beckett Street, Leeds, Yorkshire.

treatment, she was booked for surgery 5 days later. Examination at this time showed a woman of endomorphic build who had been a smoker for most of her life. Haematology and biochemical tests of hepatic and renal function were within normal limits. Radiography yielded a cardiac-thoracic ratio of upper normal limits and respiratory function tests were unremarkable. There was no clinical evidence of heart failure. The ECG showed sinus rhythm at 75 beats/minute with a normal axis and configuration. Blood pressure in her right arm was 180/80 mmHg which was considered acceptable in view of her anxiety about the forthcoming procedure.

She received diazepam 10 mg as premedication. Prior to induction intravenous and intra-arterial cannulae were placed using 1% plain lignocaine before insertion. Her blood pressure immediately prior to induction had increased to 200/90 mmHg. Anaesthesia was induced with etomidate 0.3 mg/kg via the intravenous infusion, followed shortly afterwards by atracurium 0.8 mg/kg. Ventilation of the lungs using a Mapelson A system with 100% oxygen was commenced prior to tracheal intubation.

However, before this was even attempted, she was noted to be increasingly hypertensive. By 2 minutes after induction her systolic arterial pressure was 280 mmHg. She was given phentolamine 10 mg at this time and a further 10 mg when her arterial pressure was 340 mmHg systolic. The highest systolic pressure recorded was 350 mmHg, but decreased over the next 3 minutes to 180 mmHg systolic and then settled at 150/80 mmHg by 15 minutes after induction. During this time her heart rate increased from 60 to 130 beats/minute. Sinus rhythm was present throughout and there was no electrocardiographic evidence of ischaemic changes. Tracheal intubation was not attempted until she was normotensive and was achieved without cardiovascular change. The procedure was cancelled and her lungs ventilated with nitrous oxide in oxygen until the atracurium was eliminated. Follow-up did not reveal any neurological or cardiovascular sequelae to this event. She underwent surgery 3 weeks later, which was performed uneventfully with an anaesthetic sequence of methohexitone, fentanyl, alcuronium and halothane, but she died shortly afterwards from disseminated carcinomatosis.

Discussion

Monoamine oxidase is widely distributed throughout the body and deactivates many amine-containing compounds. There may be a number of interactions which are undesirable because of this lack of specificity. At least part of the effect is to increase intraneuronal transmitter and therefore, with appropriate stimulation, larger amounts than expected may be released. With regard to anaesthesia it has been recommended that MAOIs be discontinued for 2–3 weeks prior to the procedure.[1] The rationale for this is that MAOIs irreversibly bind to monoamine oxidase and this time course is required for the generation of new enzyme. A number of interactions have been described that include both hypo- and hypertension, hyperpyrexia, convulsions, coma and hepatotoxicity.[2] Some of these can be explained by reduced metabolism of a drug or by indirect sympathomimetic actions of that drug, whilst others remain as yet unclear in their aetiology.

The use of MAOIs in clinical practice has decreased in the past decade with the recognition of their possible interactions, yet they remain useful in certain conditions. The development of newer specific MAO-A and MAO-B inhibitors may herald a resurgence of their use. These patients may present for emergency surgery where these drugs have not been discontinued.

When any anaesthetic technique is considered, one is often swayed by the hazards or side effects of such a course. A review of adverse drug reactions with MAOIs[3] revealed potential interaction with barbiturates, anticholinergics, suxamethonium, narcotic analgesics and pressor agents. However, Michaels *et al.*[4] reported uneventful induction of anaesthesia for cardiac surgery using morphine/hyoscine premedication, induction of anaesthesia with fentanyl, and tracheal intubation with the aid of suxamethonium. In two studies by El Ganzouri *et al.*,[5,6] 27 and 6 patients respectively receiving chronic MAOI therapy were anaesthetised with a variety of techniques that included thiopentone, etomidate, suxamethonium, pancuronium, morphine, fentanyl, halothane or enflurane. No patient suffered adverse effects attributable to their MAOI therapy. Similarly, Braverman *et al.*[7] showed no adverse effects in enflurane anaesthetised dogs pretreated with tranylcypromine who were then given fentanyl, noradrenaline and

adrenaline sequentially. They considered that these results supported the recommendations of El Ganzouri *et al.*[5,6] that MAOIs need not be discontinued pre-operatively.

The reasons for the rapid increase in blood pressure seen in this case report are obscure. The temporal relationship to induction of anaesthesia strongly suggests a cause and effect relationship. Etomidate, chosen for its cardiovascular stability, has been used without problem in patients receiving tranylcypromine. It would seem difficult, therefore, to attribute the cause to this agent. The use of atracurium has not been reported in patients on MAOIs but a mechanism for its interaction is not readily apparent. The clinical picture was of sudden sympathetic discharge but this occurred before any painful stimuli or laryngoscopy. There was no evidence for a phaeochromocytoma or other amine-secreting tumour found after anaesthesia or at autopsy.

Atracurium had only recently been introduced at that time and information on its clinical effects was necessarily limited. The lack of adverse reports on its use and lack of theoretical interaction made atracurium an attractive choice. If MAOIs can be safely withdrawn prior to surgery it is probably wisest to do so. However, a satisfactory technique must be found in patients who present either as emergencies or in those for whom, because of their psychiatric condition, these drugs cannot be safely discontinued. This could be achieved with diazepam for premedication and either thiopentone or etomidate for induction. Muscle relaxation may be achieved with suxamethonium or pancuronium as indicated and anaesthesia maintained with halothane or enflurane. If a narcotic is required, fentanyl in judicious quantities appears to be tolerated well.

Finally, there is the question of monitoring. A knowledge of the possible, although unexpected, interactions allowed appropriate pre-induction monitoring and the ready availability of the necessary drugs for management. The short time course of this interaction would otherwise have made detection and treatment possibly fatally late.

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CASE REPORT

Value of pre-operative carotid sinus massage

I. McCONACHIE

Summary

The usefulness of carotid sinus massage in pre-operative assessment is discussed with case examples. The technique and risks of carotid sinus massage are described. Carotid sinus massage is of particular value in the demonstration of sino-atrial and atrioventricular node disease in the absence of definitive abnormalities on the routine resting electrocardiogram, and in the identification of patients who show a hypersensitive response to vagal stimulation. These patients should be identified prior to procedures that involve marked vagal activity, since prolonged sinus arrest may occur.

Key words

Heart; sino-atrial node, atrioventricular node.

Sick sinus syndrome (SSS), or sino-atrial (SA) node disease, occurs mainly in elderly patients. Symptoms may be intermittent and may result from both brady- and tachydysrhythmias. Symptoms may include dizziness, fatigue, fainting, angina, palpitations and increasing breathlessness. However, electrocardiographic (ECG) changes may precede symptoms. Antidysrhythmic drugs and antihypertensives, such as methyldopa, may precipitate symptoms of SA node dysfunction. The ECG may show evidence of sinus bradycardia which may be inappropriate, for example, in the presence of severe pain or drugs that normally increase heart rate. Block of the SA node and arrest and atrioventricular (AV) junctional rhythms are also common. However, patients with SA node disease may have a normal routine resting ECG[1] (especially if there is only intermittent conduction disease).

It is important to identify SA disease as this may have considerable anaesthetic implications. Indeed, it has been suggested that patients with suspected SA node disease should have 24 hours of ECG monitoring prior to surgery, because vagal influences may produce prolonged sinus arrest.[2]

Recently, I have seen three cases where carotid sinus massage during pre-operative ECG recording confirmed the presence of severe SA node disease.

Case histories

Case 1

A 69-year-old man presented for elective vascular surgery. He had severe peripheral vascular disease but no obvious signs or symptoms of ischaemic heart disease and was generally quite fit. Pre-operative ECGs showed varying rates of sinus bradycardia. Carotid sinus massage on the right side caused a period of sinus arrest of 6 seconds. The operation was performed under

I. McConachie, MB, ChB, Registrar, Department of Anaesthetics, Hope Hospital, Salford M6 8HD.

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cover of a temporary transvenous pacemaker. The pacemaker was set 'on demand' and functioned intermittently throughout the operation.

Case 2

A 78-year-old man presented for cystoscopy. There were no symptoms of intercurrent cardiac disease apart from occasional dizziness, one previous fall (query blackout) and mild exertional dyspnoea. Physical examination was normal. Pre-operative ECGs showed sinus dysrhythmia with a rate that varied between 55 and 70 beats/minute and a possible old anterior myocardial infarction. Carotid sinus massage on both sides produced a nodal bradycardia of 30 beats/minute. The operation was deferred for further cardiological assessment which resulted in insertion of a permanent pacemaker.

Case 3

An 83-year-old female presented for emergency internal fixation of a fractured neck of femur. The patient was confused and denied any cardiac symptoms, but admitted to falls at home. An ECG showed 1st degree heart block and a sinus bradycardia of 55 beats/minute despite some distress due to pain. Pre-operative right carotid sinus massage caused 5 seconds of sinus arrest. The operation was performed and sinus arrest occurred at induction, and was promptly treated with intravenous isoprenaline which had been diluted and labelled previously. An oesophageal pacemaker was inserted after induction of anaesthesia, since oesophageal pacemakers have been shown to be reliable for control of intra-operative heart rate.[3] Reversal with neostigmine was not attempted, in view of the potential problems. Despite this there were several episodes of Mobitz Type II heart block at extubation.

Carotid sinus massage allowed prediction of the potential problems in this case and modification of the anaesthetic technique. It could then be ensured that appropriate monitoring, drugs and equipment were available at all times.

None of the above patients had obvious electrolyte problems, history of drug therapy (e.g. digoxin, beta-blocker, calcium antagonist therapy) or obvious hypothyroidism or hypothermia to explain their conduction problems. None of the patients had definite symptoms of severe cardiac disease. Pre-operative ECGs suggested possible SA node disease and this was confirmed by carotid sinus massage.

Discussion

The carotid sinuses are the principal baroreceptors in the body and initiate reflexes that slow the heart rate, often change the heart rhythm and cause a fall in blood pressure. The carotid sinuses are located at the origins of the internal carotid arteries and are supplied by the glossopharyngeal nerve. Stimulation by carotid sinus massage results in activation of cardioinhibitory stimuli and an inhibition of sympathetic activity similar to the effects of vagal stimulation or the administration of drugs with muscarinic properties. This may slow or stop discharge of the SA node and thereby result in sinus bradycardia or arrest, slow conduction from the SA node to the atria and produce SA block. It may also depress the AV node and inhibit AV conduction, which induces or increases AV block, decrease atrial excitability, or produce negative inotropic effects on atrial and ventricular contraction.

Most physicians would accept bradycardias below 40 beats/minute, increased level of AV block and sinus arrest of greater than 3 seconds during carotid sinus stimulation, as evidence for an AV conduction defect, carotid sinus hypersensitivity or SA node disease.

The main clinical diagnostic value of carotid sinus massage is that it aids interpretation due to AV or SA node disease and increases AV block to aid diagnosis of tachycardias.

Carotid sinus massage has considerable therapeutic value in the termination of paroxysmal supraventricular tachycardia and has also been used to terminate pain from angina pectoris, due to its effect on heart rate and myocardial oxygen demand. Similarly, massage of the carotid sinus has been reported to relieve acute pulmonary oedema. Development of AV block or ectopic beats during stimulation has been claimed to be a guide to early detection of digoxin toxicity.

However, it is as an aid to demonstrating the presence of bradydysrhythmias, that carotid sinus massage should be of value to anaesthetists. By mimicking the effects of vagal stimulation, it may identify patients who are markedly sensitive to parasympathetic over-

activity. Patients highest at risk are those who undergo anaesthesia for procedures that involve parasympathetic stimulation, such as cystoscopy and ophthalmic operations. Intra-operative bradycardia due to SA node disease may not respond to atropine.[4] Indeed, an atropine challenge has been proposed as useful in the diagnosis of sick sinus syndrome. Halothane decreases both SA and AV node conduction and may precipitate bradycardias or high AV block.[5] Neuromuscular blocking agents, such as pancuronium, which cause tachycardia due to reduced vagal and increased sympathetic activity, may offer some protection but should not be relied upon.

Technique of carotid sinus massage[6]

The patient should be supine to minimise the risk of syncope. Massage of the right carotid sinus is usually more effective than the left and should generally be performed first. Stimulation should be applied over the pulsation of the carotid artery just below the angle of the jaw at the upper level of the thyroid cartilage. It is a matter of personal preference whether the thumb or the index and middle fingers are used. Gentle stimulation should always be performed initially, as some elderly patients have hypersensitive carotid sinuses and prolonged sinus arrest is possible. Carotid sinus massage should only be performed for 5 seconds at a time to avoid prolonged interruption of cerebral blood flow. Nevertheless, carotid sinus massage should usually be avoided in patients with a history of cerebrovascular accident or transient ischaemic attacks, and carotid bruits should always be sought. Simultaneous bilateral carotid sinus massage is absolutely contraindicated. The chance of problems is rare, but facilities for resuscitation should always be available. An ECG rhythm strip should be recorded during carotid sinus massage to detect abnormalities and to enable a permanent record to be kept.

Hazards of carotid sinus massage

Irreversible asystole following carotid sinus massage has been reported only once.[7] Prolonged sinus arrest may be terminated by getting the patient to cough or by a sharp blow to the precordium. Instances of ventricular tachycardia and ventricular failure after carotid sinus massage are exceedingly rare.

Cerebral effects, such as mono- or hemiplegia, should be rare if proper precautions with technique are taken, and are often transient in any case. They may be due to a reduction of cerebral blood flow or to dislodgement of atheromatous plaques. Many workers have used carotid sinus massage extensively as a diagnostic test and the risks with properly performed massage are extremely small.[7]

In conclusion, I suggest that carotid sinus massage (with simultaneous recording of ECG rhythm strip) is an important part of the anaesthetic assessment of patients with suspected SA node disease and may be a practical alternative to 24-hour ECG recordings. It is of particular value in the assessment of patients who have only minor abnormalities on their routine resting ECG but have symptoms suggestive of SA or AV node disease and who may be markedly sensitive to parasympathetic stimulation. It is important that patients at risk are identified and, if necessary, have a prophylactic pacemaker inserted. The opinion of a cardiologist should be sought if problems are anticipated and, if necessary, temporary or permanent pacemaker implantation.

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CASE REPORT

Paroxysmal nocturnal haemoglobinuria

Peri-operative management of a patient with Budd–Chiari syndrome

M. B. TAYLOR, J. G. WHITWAM AND A. WORSLEY

Summary

The peri-operative management of a patient with paroxysmal nocturnal haemoglobinuria and associated hypoplastic anaemia, who underwent successful elective surgery for the complication of Budd-Chiari syndrome, is described. Anaesthesia in patients with paroxysmal nocturnal haemoglobinuria should be based on drugs and materials least likely to cause complement activation. The reasons for use of a technique based on benzodiazepines, opioids, isoflurane and the avoidance of nitrous oxide are discussed.

Key words

Blood; haemoglobinuria, coagulopathy.

Paroxysmal nocturnal haemoglobinuria is a rare, acquired, chronic haemolytic anaemia. It is associated with a clonal bone marrow stem cell abnormality which leads to production of erythrocytes, granulocytes and platelets with membrane defects that confer an abnormal sensitivity to lysis by complement. It has been shown recently that the membrane abnormality may be a deficiency of decay accelerating factor, a membrane regulatory protein of complement.[1]

Patients with this condition may have all the clinical and laboratory signs of a chronic haemolytic anaemia, together with haemoglobinuria which may be infrequent and rarely occurs at night, a bleeding tendency (from thrombocytopenia) and signs of venous thrombosis. The latter, which may be caused by abnormal platelet function, may contribute to the impaired renal function which is often present and causes some of the commonest clinical symptoms, for example, abdominal pain. Hepatic vein thrombosis is a common complication with a high mortality rate[2] and surgery for this condition is associated with a high peri-operative mortality.[3,4] There are very few references to the anaesthetic management of patients with paroxysmal nocturnal haemoglobinuria,[5] although one case report[6] suggests that activation of complement and a haemolytic episode during the induction of anaesthesia were partly responsible for the patient's cardiac arrest.

Case history

A 27-year-old male, who weighed 56 kg, had a 4-year history of hypoplastic paroxysmal nocturnal haemoglobinuria complicated by intermittent episodes of abdominal pain, and later developed respiratory embarrassment due to abdominal ascites. The clinical diagnosis of

M.B. Taylor, MB, BS, FFARCS, Senior Registrar, J.G. Whitwam, MB, ChB, PhD, FRCP, FFARCS, Professor of Clinical Anaesthesia, A. Worsley,* BSc, MB, BS, MRCP, MRCPath, Leukaemia Research Fund Fellow, Departments of Anaesthetics and Haematology, Royal Postgraduate Medical School, Du Cane Road, London W12 OHS.

* Present appointment: Consultant Haematologist, Royal Victoria Hospital, Bournemouth, Hampshire.

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Budd–Chiari syndrome (hepatic vein thrombosis) was confirmed by ultrasound and venography. He was treated initially with paracentesis, intravenous heparin infusions, gut bacterial decontamination with nonabsorbable antibiotics, and bed rest. He was managed for the next 5 months by regular paracentesis, subcutaneous heparin and transfusions of washed red cells and platelets. These were administered because of recurrent severe anaemia and thrombocytopenia, and to try to suppress the abnormal bone marrow clone. Hepatic and renal function were relatively normal. It became increasingly difficult to maintain the haemoglobin level with washed cell transfusions and, in view of the large splenomegaly and probable aggravating element of hypersplenism, it was decided to remove the enlarged spleen and to perform a portocaval shunt.

Immediate pre-operative preparation included the administration of antibiotics to decontaminate the bowel and transfusions of washed red cells which increased the haematocrit from 24 to 46%.

Anaesthesia

To prevent dehydration an infusion of dextrose 4% in saline was administered overnight pre-operatively at a rate of 100 ml/hour to a total of 1.5 litres. The patient received lorazepam 2 mg for overnight sedation and a further 3 mg orally for premedication 2 hours before transfer to the anaesthetic room.

Anaesthesia was induced with midazolam 0.3 mg/kg, fentanyl 4 μg/kg and pancuronium 6 mg. The patient's trachea was intubated and his lungs were ventilated with oxygen-enriched air (F_{IO_2} 0.5) and isoflurane 1% to an end tidal carbon dioxide concentration of 4%. Anaesthesia was maintained with isoflurane 0.5–1.5%, fentanyl and pancuronium to total doses of 30 μg/kg and 0.22 mg/kg, respectively. Nitrous oxide was not administered at any stage. Three peripheral venous cannulae were introduced for possible transfusion and a further two were inserted into the right internal jugular vein. The left radial artery was also cannulated.

The end tidal carbon dioxide, inspired oxygen and isoflurane concentrations were measured throughout, together with the ECG, arterial, central venous and airway pressures and nasopharyngeal temperature. A positive end expiratory pressure of 1 kPa was maintained during the portocaval anastomosis.

Anaesthesia was uneventful but surgery was difficult. Five litres of ascitic fluid were drained at the start. Very large collateral vessels were present and, as a result, massive haemorrhage occurred during the procedure. Blood was replaced with washed red cells, human albumin solution (4.5%), fresh frozen plasma and platelets to total quantities of 22 units, 8 units, 8 units and 28 units, respectively, during the intra-operative period, which lasted approximately 3.5 hours. The values for the haematocrit at the start and completion of the procedure were 43 and 30%. Urine output was maintained at a minimum rate of 1 ml/minute with intermittent doses of frusemide (total dose 20 mg). In addition, calcium chloride and sodium bicarbonate were administered to total doses of 1.5 g and 50 mmol, respectively.

A splenectomy and side to side portocaval anastomosis were performed and the mean pressure in the portal venous system decreased from 32 to 12 mmHg.

Postoperatively the patient's lungs were electively ventilated for 4 hours and he made an uneventful recovery. Six months later, at the time of writing, he was much improved with few attacks of abdominal pain, no ascites, but still required blood and platelet transfusions.

Discussion

The principal problem in patients with paroxysmal nocturnal haemoglobinuria is the increased susceptibility of blood cells to the effects of complement. This is associated with haemolytic episodes and intravascular coagulation which usually takes the form of localised thrombotic episodes, one example of which is outlined in this report. One hypothesis for the cause of these thrombotic episodes is platelet lysis and activation. In addition, bone marrow hypoplasia is often present in these patients and results in transfusion-dependent anaemia. Transfusion is hazardous and requires the administration of carefully washed cells, since any foreign plasma may cause complement activation and haemolysis of the patient's residual red cells. If liver function is impaired then the patient will be less likely to be able to metabolise active complement fragments.

The complement proteins take part in the

Table 1. Principles of anaesthetic management of patients with paroxysmal nocturnal haemoglobinuria.

Liaison with haematologist and surgeon.

Major surgery: reduce the proportion of circulating abnormal red cells by either:
- transfusion, if anaemic;
- or exchange transfusion.

All surgery: minimise complement activation:
- avoid the intravenous route, when possible, for drugs;
- avoid drugs known to activate complement or those with a high incidence of anaphylactoid responses; avoid drugs formulated in Cremophor;
- use washed red cells for transfusion;
- prophylaxis against infection;
- avoid acidosis and hypoxia;
- reduce psychological stress, e.g. by benzodiazepine premedication;
- antibiotic gut decontamination to minimise bacterial endotoxin absorption.

Bleeding and thrombotic problems:
- avoid dehydration;
- consider the use of low doses of subcutaneous heparin;
- platelets and fresh frozen plasma may be required; use judiciously as these may themselves aggravate complement activation.

Bone marrow hypoplasia may be present, in which case the use of nitrous oxide should probably be avoided.

If associated with Budd–Chiari syndrome, hepatic function may be compromised; drugs which may damage the liver should be avoided.

acute phase response.[7] They normally decrease after induction of anaesthesia and during the first 12 hours after surgery,[8] but then increase well above pre-operative levels to a maximum on about the 4th postoperative day.[9] This may account for the reputation patients with paroxysmal nocturnal haemoglobinuria have, of developing venous thrombosis in the postoperative period; the administration of heparin together with adequate hydration may help to prevent this. Heparin inhibits complement activation[10,11] and it is used in the general management of these patients, but its administration in substantial doses intra-operatively during major surgery associated with blood loss, is not easy to justify. Moreover, protamine should not be used since heparin protamine complexes activate the classical complement pathway.[12]

The intravenous route of drug administration is associated with the highest frequency of anaphylactoid reactions, some of which involve complement activation. Many of these reactions are subclinical or of a minor nature and may remain unnoticed.[13] However, in patients with paroxysmal nocturnal haemoglobinuria, such reactions that involve complement become much more serious because of the vulnerability of the blood cells to lysis. When suitable, an inhalational induction anaesthesia or the use of conduction analgesia are theoretically the safest. However, the presence of thrombocytopenia will contraindicate some local anaesthetic techniques.

The intravenous induction agents least likely to cause anaphylactoid reactions are the benzodiazepines and the opioids, and the relatively new drug vecuronium would perhaps have been a better choice of muscle relaxant than pancuronium.

Nitrous oxide causes a reduction of methionine synthetase in the liver that leads to vitamin B_{12} deficiency and megaloblastic bone marrow changes.[14] The subject has been reviewed by Eger.[15] These changes can be reversed by the administration of folinic acid[16] but prudence suggests that it should be avoided in patients with hypoplastic anaemia, particularly if liver function may be compromised, as was the case in this patient. If severe haemolysis does develop in the peri-operative period, which is most likely in unprepared patients for emergency surgery, 250–500 ml of high molecular weight dextran (150 000) may halt the episode. This is advocated by some clinicians,[5,17] but dextrans may cause anaphylactoid reactions and they are not used in patients with paroxysmal nocturnal haemoglobinuria at this hospital.

In this case the patient also had a Budd–Chiari syndrome, in which hepatic drug metabolism may be impaired.[18] Isoflurane is the least metabolised of the volatile inhalational agents

and appears to have the lowest potential for hepatotoxicity. It is for these reasons that it was used in this patient.

The general principles of anaesthetic management of patients with paroxysmal nocturnal haemoglobinuria are outlined in Table 1. For major surgery the proportion of abnormal red cells in the blood should be reduced either by transfusion in anaemic patients[5] or by exchange transfusion[19] if the haematocrit is relatively normal, and in this sense the management is similar to that of patients with sickle cell anaemia (HbSS) prior to major surgery. All blood given to patients with paroxysmal nocturnal haemoglobinuria should be washed to remove plasma and leucocytes and thereby reduce the risk of leucocyte sensitisation, HLA antibody production and reactions which may activate complement.

Other aspects of the general management are also intended to reduce factors associated with complement activation: prevention of infections with prophylactic antibiotics, chest physiotherapy and gut decontamination with nonabsorbable antibiotics to reduce bacterial endotoxin absorption; the avoidance of drugs known to activate complement, for example, some radiocontrast media, inappropriate anaesthetic agents, and drugs formulated in Cremophor (e.g. vitamin K).[20]

In conclusion, the anaesthetist should avoid measures which are known to be associated with complement activation and be aware of the potential of these patients for haemolytic and thrombotic complications.

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CASE REPORT

Cardiovascular collapse following epidural anaesthesia for Caesarean section in a patient with aortic incompetence

J. D. ALDERSON

Summary

A death following epidural anaesthesia for Caesarean section in a patient with aortic incompetence and pre-eclampsia is described. Possible hazards of epidural anaesthesia in aortic incompetence are described and it is suggested that reduction of total peripheral resistance is contraindicated in such patients.

Key words

Anaesthetic techniques, regional; epidural.
Complications; death.

Many authorities recommend the use of epidural anaesthesia for obstetric patients with heart disease. This is a case in which institution of epidural anaesthesia was associated with cardiovascular collapse from which resuscitation was unsuccessful.

Case history

A 36-year-old primipara, weight 55 kg, initially presented at a district general hospital obstetric clinic at 16 weeks gestation. There was no significant past medical history but, on general examination, she was found to have a heart murmur and her arterial blood pressure was elevated at 220/120 mmHg. A provisional diagnosis of aortic incompetence was made on admission but there was no obvious explanation of the hypertension. Routine screening tests excluded renal disease and phaeochromocytoma. Labetalol therapy was instituted to control the hypertension but signs of heart failure became apparent and this was changed to methyldopa. Therapeutic abortion was offered but declined. Signs of heart failure that included dyspnoea on minimal exertion and paroxysmal nocturnal dyspnoea, were increasing in severity by 32 weeks gestation and necessitated transfer to a regional cardiological centre for further management.

Cardiological opinion, supported by echocardiography, suggested severe aortic valve disease, with predomination of incompetence. Echocardiography also suggested mitral incompetence and demonstrated left ventricular hypertrophy and dilatation of the ascending aorta. In addition, proteinuria of 6 g/24 hours had now developed, compatible with a diagnosis of severe pre-eclampsia in a patient with predominantly aortic incompetence. Her cardiac failure increased over the next few days, with increased weight gain, dependent oedema and dyspnoea. Joint consultation between cardiologist, obstetrician and anaesthetist decided that delivery by elective Caesarean section under epidural anaesthesia was indicated, the cardiac lesion to be further investigated by angiography once pregnancy

J.D. Alderson, MB, ChB, FFARCSI, Consultant, Department of Anaesthesia, Northern General Hospital, Herries Road, Sheffield S5 7AU.

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was over. Relevant drug therapy at this stage consisted of methyldopa 250 mg 6-hourly and frusemide 80 mg daily.

The morning dose of frusemide was omitted on the day of operation and an intravenous preload of one litre of Hartmann's solution given. Pulse and blood pressure were monitored non invasively by Dinamap and her ECG monitored continuously. A central venous pressure line was not inserted as it was thought that it would not be simple and could distress the patient, and the results would be difficult to interpret in view of the unconfirmed nature of the heart lesion. Following a test dose of 2 ml plain 0.5% bupivacaine, a further 18 ml was injected at $L_{3/4}$ as a single bolus dose via an epidural catheter with the patient wedged onto the left side, with two pillows under the head. Analgesia that extended to T_4 was achieved after 15 minutes, but sacral analgesia was absent.

Her blood pressure decreased from an initial 158/98 to 70/50 mmHg but responded to a further 500 ml of Hartmann's solution, and increased to 98/50 mmHg. A further 6 ml 0.5% plain bupivacaine was given with the patient supported sitting up to encourage caudal spread. She was again placed in the supine wedged position after 10 minutes. Her blood pressure at this stage decreased to 45/20 mmHg but pulse rate remained at the pre-epidural rate of 100–110 beats/minute. The blood pressure continued to fall to unrecordable levels despite increased intravenous fluids and ephedrine 15 mg intravenously. The patient became drowsy and finally unconscious.

Her trachea was immediately intubated, the lungs ventilated with 100% oxygen and cardiac massage begun. ECG monitoring now showed widening of the complexes consistent with myocardial ischaemia and, eventually, ventricular fibrillation. Standard resuscitation measures, including cardiac massage, ventilation with 100% oxygen, defibrillation, intravenous adrenaline, calcium chloride and lignocaine, were initially successful in producing maternal pulses. As the fetal heart was audible by ultrasound probe, the decision was made to proceed with the Caesarean section. A live male infant, weight 1.6 kg, Apgar score 1 at one minute, was delivered but the maternal ECG complexes further deteriorated and became wide and bizarre, indicative of severe myocardial ischaemia.

Cardiac massage remained effective in producing a cardiac output and was used throughout the operation but a spontaneous output could not be maintained and it was reluctantly agreed to discontinue attempts at resuscitation after 1 hour 10 minutes.

Postmortem examination confirmed the presence of hypertrophy of the left ventricle and demonstrated ischaemic changes of the inner third of the myocardium. The mitral valve appeared normal. The aortic valve had normal cusps separated by dilatation of the aortic ring to produce aortic incompetence; the internal diameter of the valve was 2.5 cm. The coronary arteries appeared normal. The ascending aorta was diseased with atheroma which extended into the upper abdominal aorta. There was no evidence of renal disease.

The baby was discharged from the neonatal intensive care unit at 7 days, after therapy for birth asphyxia (including 5 hours of artificial ventilation), hypothermia and jaundice. He appeared normal neurologically.

Discussion

The physiological changes of pregnancy are well established, as are the effects on these of epidural anaesthesia.[1] The increased cardiac work required by pregnancy may precipitate cardiac failure in patients with heart disease. It is generally accepted that it is wise to admit patients with symptomatic cardiac disease to hospital for some time prior to delivery.[2] For labour, epidural analgesia has advantages, in that complete analgesia relieves anxiety, apprehension and unnecessary activity and so prevents the development of tachycardia, hypertension and increase in cardiac output.[2]

Caesarean section is thought by some to be the treatment of choice in the severely ill pregnant cardiac patient.[2,3] Bonica and Ueland[2] suggest that balanced general anaesthesia may be the method of choice for patients with aortic stenosis, congenital heart disease and severe coronary artery disease, and in those in whom profound vasomotor block is to be avoided, but suggest that regional anaesthesia (subarachnoid or epidural) may be used in other cardiac disorders provided severe hypotension is avoided. Joyce[4] and Mangano[5] suggested that aortic insufficiency is improved by lowering the systemic vascular resistance, which decreases regurgitation. A small study[6] of volunteers with epidural

blocks to the level of T_5 or above, suggested greater reduction in total peripheral resistance when adrenaline is added to local anaesthetic solution than without (-39.6% change compared with -2.9%). Adrenaline-free solution was used in the patient reported here.

Subendocardial ischaemia can be provoked in dogs with normal coronary arteries by reduction of the end diastolic pressure.[7] Studies have shown that phasic coronary flow is mainly systolic in severe aortic incompetence, with a markedly reduced diastolic coronary blood flow.[8,9] This may lead to a mean reduction of coronary blood flow,[7,8] with reversed flow during part of diastole.[10] Furthermore, Buckberg[7] showed that regional distribution of coronary blood flow is abnormal in severe aortic incompetence, with the endocardium underperfused at the expense of the epicardium.

A case was reported of the surgical correction of coarctation of the aorta in a patient who also had aortic incompetence, where reduction of the peripheral resistance following surgical correction led to cardiac failure which was reversible when the peripheral resistance was increased again by partially clamping the aorta.[11] It was suggested that in cases with aortic incompetence and coarctation, the former should be corrected first, as the coronary flow in aortic incompetence is improved by high peripheral resistance.

In the case reported here it is postulated that the reduction in peripheral resistance following institution of the epidural block, produced hypotension due to peripheral vasodilatation and hence reduced coronary blood flow. This is supported by the ischaemic ECG appearance and by the postmortem appearance of an ischaemic inner myocardium. It is possible that the resultant cardiac failure might have been reversible had the peripheral resistance been increased with α-adrenoreceptor stimulants.

Cardiac massage proved successful in maintaining an output. This suggests that hypovolaemia was not a contributory factor. The total amount of fluid given was 6 litres, mostly during attempts at resuscitation. It was known that the patient was on the verge of cardiac failure, required diuretics and was therefore unlikely to be hypovolaemic pre-operatively.

It is suggested that epidural anaesthesia may be contraindicated for Caesarean section in patients with symptomatic aortic incompetence.

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CASE REPORT

Phaeochromocytoma as a cause of pulmonary oedema

H. J. BLOM, V. KARSDORP, R. BIRNIE AND G. DAVIES

Summary

Phaeochromocytoma can mimic many serious disease entities. This report describes a 43-year-old man who presented with pulmonary oedema due to a phaeochromocytoma. Predominantly adrenaline-secreting tumours seem to predispose to this complication. Labetalol, a combined alpha- and beta-receptor blocker, should be considered as the initial treatment in these cases and continued during surgery.

Key words

Complications; pulmonary oedema.
Surgery; phaeochromocytoma removal.

Pulmonary oedema can be classified into cardiac and non-cardiac types. The latter is mostly referred to as the acute respiratory distress syndrome (ARDS).[1] Among the cardiac causes of pulmonary oedema, none of the standard textbooks considers a phaeochromocytoma. The sparse literature on this subject[2–4] suggests predominantly adrenaline-producing phaeochromocytoma as the cause of this complication. Phaeochromocytoma can also mimic various disease entities such as pulmonary oedema,[5] myocardial infarction,[6] septicaemia[7,8] or an acute abdominal problem.[6,9–11] The following report describes a patient who presented with pulmonary oedema.

In this patient two specific features are stressed. First, the high adrenaline levels and second, the successful treatment with labetalol. These aspects are reviewed.

Case history

An athletic 43-year-old computer operator presented with rapidly progressive dyspnoea, precordial pain, nausea and vomiting. Physical examination showed an ill, dyspnoeic and thirsty man, with profuse perspiration. The pulse rate was 130 beats/minute, regular, and arterial blood pressure was 150/100 mmHg. Auscultation of the chest elicited scattered bilateral râles but normal cardiac features. The electrocardiogram was normal except for signs of left atrial strain. Chest radiography (Fig. 1) showed a butterfly-like distribution pattern typical of pulmonary oedema. Laboratory values on admission were essentially normal. The clinical picture rapidly deteriorated into shock and he required artificial ventilation of his lungs 10 hours after admission. Respiratory assistance was given with 0.5–1.0 kPa positive end expiratory pressure.

H.J. Blom, MD, Consultant Physician, Department of Internal Medicine, V. Karsdorp, MD, Junior Registrar, R. Birnie, MD, Nephrologist, G. Davies, FRCP, Department of Radiology, St Lucas' Hospital, Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands.

Correspondence should be addressed to: Dr H.J. Blom, Departments of Internal Medicine and Intensive Care, St Lucas' Hospital, Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands.

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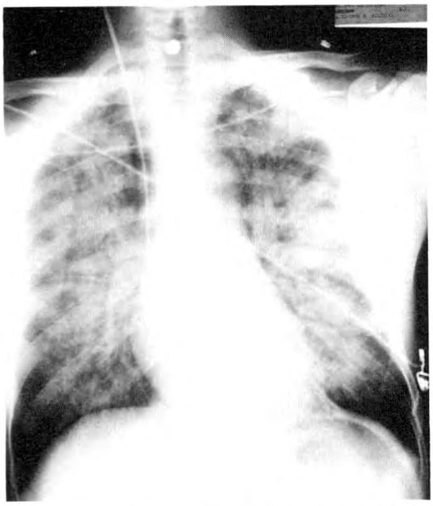

Fig. 1. Chest radiograph 10 hours after admission showing pulmonary oedema with butterfly-like distribution. Swan–Ganz catheter *in situ*.

Initially no measurable blood pressure could be recorded with the intra-arterial line (radial artery). There was partial renal failure for about 24 hours, expressed by oliguria, albuminuria and a rapid increase of serum creatinine levels. Medical treatment was instituted with methylprednisolone 2 g, dobutamine (up to 750 μg/minute) and dopamine (up to 1000 μg/minute). All common causes of cardiac and non-cardiac pulmonary oedema could be virtually excluded.

An interview with his girlfriend revealed regular episodes of palpitations associated with heavy sweating during the previous half year. This suggested a phaeochromocytoma and vanillic mandelic acid (VMA) determinations showed excessive adrenergic activity. The elevated levels of homovanillic acid (HVA), which represent the catecholamine metabolite of dopamine, disappeared after cessation of dobutamine and dopamine.

The clinical picture was consistent with a predominantly adrenaline-secreting tumour; therefore labetalol 5 mg intravenously was started. Subsequently, ultrasound/CT imaging (Fig. 2) and scintiscan (with 1.15 mCi ^{131}I-*meta*-iodobenzylguanidine (MIBG), Fig. 3) showed a phaeochromocytoma in the left adrenal gland.

The patient was discharged without further complaints after uncomplicated surgical removal, also under labetalol protection, although follow-up with ^{131}I-MIBG for metastatic disease will be performed because the histology showed vessels that contained tumour cells. Values of catecholamines and metabolites, shown in Table 1, proved the predominantly adrenaline-secreting nature of the tumour. The same ratios of catecholamines were measured in the supernatant of homogenised tumour tissue.

Discussion

Phaeochromocytomata are tumours of the adrenal medulla cells that secrete catecholamines. Both adrenaline and noradrenaline lead to an elevation of blood pressure as a result of their action on the heart and blood vessels. Varying degrees of imbalance between endogenous vasodilator substances and levels of circulating catecholamines may account for the lack of relation between the prevailing levels of plasma catecholamines and the height of the blood

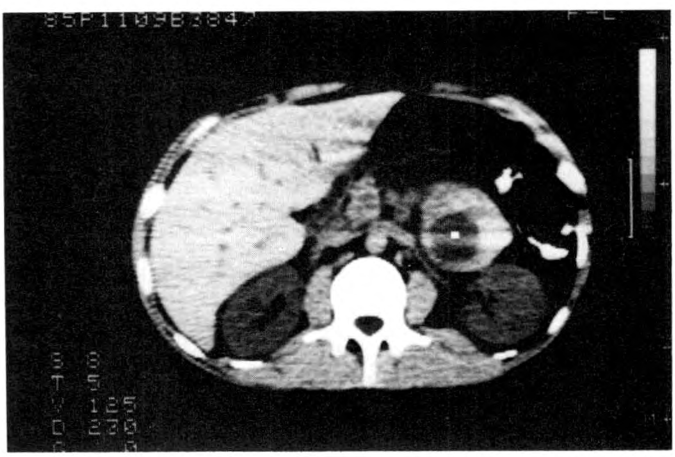

Fig. 2. CT imaging of the tumour in the left adrenal gland showing clearly its size and the central necrosis.

Table 1. Urine catecholamines and metabolites.

	Normal values (mmol/g creatinine)	Patient values 10th day	Patient values 16th day
Adrenaline	16–92	3454	4896
Noradrenaline	62–370	4322	1975
Dopamine	609–4189	1569	1363
Normetanephrine	18–178	1703	258
Metanephrine	59–480	4733	10 900
3-Methoxytramine	65–619	240	350
Vanillyl mandelic acid	<3 mmol/mol creatinine	Between 12 and 20 (12 determinations)	
Homovanillic acid	Elevated only during dopamine/dobutamine treatment (days 1 and 2)		

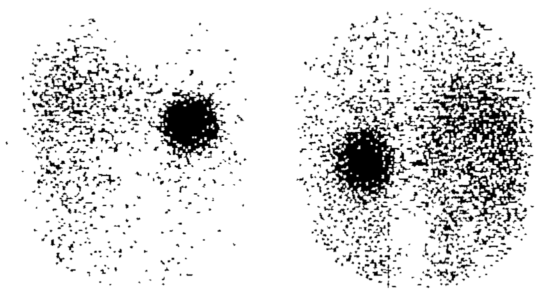

Fig. 3. ^{131}I-MIBG scintiscan showing massive accumulation of the tracer in the tumour, at the level of the left adrenal gland.

pressure.[12] In addition, the concomitant secretion of dopamine may counteract the vasoconstrictive effects of noradrenaline.[13] The most classic clinical features of this tumour are headache, palpitations and excessive and inappropriate sweating.[14] Less commonly encountered symptoms are nausea, vomiting and chest pains as seen in our patient. Only a few reports cite pulmonary oedema as a leading symptom.[2–4] In these cases predominantly adrenaline-secreting tumours were found and thought responsible for the cardiac type of pulmonary oedema. The clinical picture and laboratory results of our patient (Table 1) support this concept.

Pathophysiologically, the most plausible cause of the pulmonary oedema is left ventricular failure. The paroxysmal hypertension causes an increase in end diastolic pressure and an increase in the microvascular hydrostatic pressure which is clinically represented in an elevated pulmonary capillary wedge pressure (PCWP). Measurements of the PCWP during attacks in our patient reached levels of 18 mmHg; at the same time the central venous pressure reached values of 20 cm H_2O. Both values became normal after an attack. Intra-arterial pressure at the level of the radial artery was not detectable, probably because of the extreme vasoconstriction during attacks.

Cardiac complications of phaeochromocytoma were reviewed by Northfield[15] and include a wide range of cardiac dysrhythmias. Electrocardiographic abnormalities that included deep Q-waves, ST elevation and T-wave inversion, were described in patients without coronary disease.[15] More distinct abnormalities have been described, such as focal catecholamine myocarditis[16] and functional obstruction of the left ventricular outflow tract by hypertrophic obstructive cardiomyopathy.[17] Labetalol is a combined alpha- and beta-blocking agent, which is most potent for its beta-adrenoreceptor blocking activity. The use of labetalol in phaeochromocytoma was first reported in 1976[18] and proved successful in four out of five patients; one patient required additional alpha blockade. Several reports which confirmed this observation appeared within the next few years.[19–21] In one multicentre trial, 21 out of 30 phaeo-

chromocytoma patients showed good blood pressure control with labetalol. The drug's effect appeared to be better in predominantly adrenaline-secreting tumours.[22]

Theoretically, if a phaeochromocytoma secretes predominantly noradrenaline (as in most cases), labetalol may provide insufficient alpha blockade.[21] Inadequate alpha-adrenergic blockade could aggravate hypertensive reactions by the unopposed post-synaptic alpha-receptor effect during adequate beta-receptor blockade. This sometimes requires additional alpha blockade with phentolamine.[23] Pre-operative preparation and intra-operative management of patients with phaeochromocytoma with labetalol, seem to be simpler and safer than previous techniques with separate alpha- and beta-adrenoreceptor blocking agents.[22,24,25]

Any patient who develops an unexplained cardiac-type pulmonary oedema, may have a phaeochromocytoma. In these predominantly adrenaline-producing tumours labetalol may be the treatment of choice. In addition, localisation and follow-up with ^{131}I-MIBG is a helpful and theoretically attractive new diagnostic technique which may also have its place in the treatment of metastatic disease.[26,27]

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CASE REPORT

A nasal adhesion following prolonged nasotracheal intubation

K. M. SHERRY AND A. MURDAY

Summary

A patient who presented with nasal obstruction 4 months after prolonged pernasal tracheal intubation is described. The cause of the obstruction was an adhesion which extended from the septum to the inferior turbinate. The evidence in support of long-term pernasal tracheal intubation is presented and the aetiology of this complication is discussed.

Key words

Intubation, nasotracheal; complications.

Plastic tracheal tubes which cause less tissue reaction than rubber ones, have been available for use since the early 1960s. Since their development there has been a trend away from tracheostomy and towards oral or nasal tracheal intubation for patients who require long-term respiratory support.[1-3] Both the use of soft plastics which mould to the airway contours and the development of high volume, low pressure cuffs, have contributed to a dramatic decrease in the incidence of intubation-related complications. However, a patient is described who developed a nasal adhesion following 20 days of nasotracheal intubation. The condition presented after his inpatient discharge and required operative treatment.

Case history

A 64-year-old male was admitted for elective replacement of a mechanical mitral valve prosthesis by a Carpentier–Edwards xenograft. Nine years before admission he had undergone surgery for symptomatic rheumatic mitral valve disease and a Star Edwards valve was inserted. Postoperatively he had developed a mild right hemiparesis from which he made a good recovery, and maturity onset diabetes which was controlled with metformin and chlorpropamide. He suffered from repeated systemic emboli in the 9 years prior to this admission, despite warfarin therapy. He had no other significant past medical history; however, he had been a boxer as a child.

On pre-operative assessment he was clinically well and maintained on oral hypoglycaemic and anticoagulant therapy. Anaesthesia was induced using a thiopentone, opioid relaxant sequence and the trachea was intubated perorally using a size 9-mm Portex blue line cuffed tracheal tube. His mitral valve was replaced during hypothermic cardiopulmonary bypass with his core temperature maintained at 27°C. He had a history of a previous intracerebral event and so, at the

K.M. Sherry,* FFARCS, A. Murday, FRCS, Senior Registrars, The London Chest Hospital, Bonner Road, London E2.

* Present appointment: Senior Registrar, The Middlesex Hospital, London W1.

Correspondence should be addressed to K.M. Sherry, 55 Higher Drive, Purley, Surrey CR2 2HR.

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onset of cardiopulmonary bypass, methylprednisolone 2 g and mannitol 20 g were infused. Extracorporeal perfusion was withdrawn without difficulty following replacement of the valve, surgery was completed and he was transferred to the intensive care unit.

Recovery was complicated by continuing blood loss so that his chest was re-opened 4 hours postoperatively and further haemostasis secured. An infusion of dopamine 5 μg/kg/minute was required for 16 hours following surgery, to improve his urine output. He was fully conscious but had developed a left hemiparesis by the morning after surgery. His heart was in sinus rhythm and his circulation was stable; respiratory gas exchange and urine output were good. The dopamine infusion and ventilation of the lungs were discontinued, the trachea was extubated and he was returned to the ward.

Eight days later he was re-admitted to the intensive care unit with a complicated clinical picture of rapid atrial fibrillation, pulmonary oedema, unstable diabetes and dehydration. Arterial blood gas analysis revealed an arterial oxygen tension ($Pa\text{O}_2$) of 6.7 kPa and carbon dioxide tension ($Pa\text{CO}_2$) of 6.7 kPa on an inspired oxygen concentration of 28%. The trachea was intubated using an 8-mm Portex profile cuffed nasotracheal tube introduced through the right nostril, and therapy by intermittent positive pressure ventilation commenced. A 12-FG nasogastric tube was introduced via the left nostril to permit supplementation of oral feeding. His clinical condition improved with rehydration and digoxin to control his ventricular rate and insulin to control his blood sugar. He did not require additional circulatory support; however, he had persistent pulmonary interstitial oedema which was slow to resolve. A $Pa\text{O}_2$ of 10 kPa was achieved during intermittent positive pressure ventilation with a fractional inspired oxygen concentration of 0.4, but he failed to maintain adequate spontaneous ventilation and received some form of ventilatory support via the same nasotracheal tube for a total of 20 days. At no time during the period of tracheal intubation was any significant bacterial growth cultured from his regular nasal swabs, sputum or blood samples, nor did he complain of nasal discomfort.

He was well when discharged from hospital 34 days after his surgery. At his first outpatient appointment, he did not comment on any problems related to his nose although he did require the removal of a painful sternal wire. For this general anaesthesia was provided by thiopentone, nitrous oxide in oxygen and enflurane and he breathed spontaneously and without obstruction through a mask and Magill system. Four months later he complained of increasing difficulty with nasal breathing, especially at night, and a specialist clinical opinion was sought. His columnella was dislocated to the left and he had an adhesion within the right nasal cavity that extended from the septum onto the right inferior turbinate. This was divided under local anaesthesia and a stent was inserted which remained *in situ* for one week. Examinations over the ensuing 6 months revealed no recurrence of nasal adhesions.

Discussion

There has been a tendency to use oral or nasal tracheal intubation [1–3] for prolonged respiratory support and to avoid tracheostomy,[4] following the development of plastic tracheal tubes with their high volume, low pressure tracheal cuffs. Many clinicians still believe that protracted translaryngeal tracheal intubation is likely to cause laryngeal injury; however, this has not been substantiated by surveys which have found no association between the duration of oral or nasal tracheal intubation and the severity of laryngotracheal injury.[5,6] Comparisons between oro- and nasotracheal intubation have shown that there is a higher incidence of ulcers on the posterior wall of the glottis following peroral intubation.[5,7] For this reason many anaesthetists elect to intubate the trachea pernasally in intensive care patients. Several local complications have been described in association with pernasal intubation. Direct trauma during the intubation can cause bleeding,[5] turbinectomy [8,9] and retropharyngeal perforation.[10] Complications that result from the prolonged presence of a nasal tube have included ulceration and necrosis on the inferior turbinate,[6,11] nasal septum[5] or ala nasi,[12,13] perforation of the nasal septum,[6] purulent nasal infection,[5] facial sinusitis [14–16] and damage to the Eustachian tube.[9,13] Persistent and late complications are uncommon; however, a synechia between the nasal septum and inferior turbinate, which resolved spontaneously, has been previously described.[6]

Two factors which predispose to the formation of adhesions are trauma and infection. It is likely that this patient, with his history of boxing, suffered repeated blows to the face that led to a distortion of the nasal cavity and this is supported by the dislocation of his columnella. There was no obvious haemorrhage but, with a distorted nasal cavity, he had an increased risk of trauma on initial intubation and of necrosis from the prolonged pressure of a pernasal tube on promontories within the nose. During the immediate postoperative period he required a dopamine infusion for the treatment of inadequate urine production, despite an adequate circulating volume. Poor urine output following cardiac surgery often indicates a low cardiac output and a consequent decrease in tissue perfusion. Furthermore, he had developed a dysrhythmia and cardiac failure in the 9 days after surgery. Low cardiac output in addition to the obligatory catabolic status following surgery, reduces the ability of the body to maintain the integrity of tissues and increases the tendency to develop pressure damage. In this case no pathogens were cultured from frequent nasal swabs and at no time did he complain of nasal or facial discomfort, but patients with cardiac failure and diabetes have an increased risk of developing secondary infection in traumatised tissue.

The underlying aetiology of the adhesion in this patient is therefore likely to have been pressure damage to the nasal mucosa overlying the septum and inferior turbinate, and the subsequent formation of granulation tissue which organised into a fibrous band. Further factors which may have predisposed to the formation of the adhesion are trauma on intubation and nasal infection.

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CASE REPORT

Abscess following cannulation of the radial artery

S. L. LINDSAY, R. KERRIDGE AND B-J. COLLETT

Summary

Local abscess formation, septicaemia and median nerve palsy occurred as complications of radial artery cannulation in a 24-year-old man with malaria. The case is described and the nosocomial infection hazard of arterial cannulation is discussed.

Key words

Monitoring; blood pressure.
Complications; nerve damage.

Direct monitoring of arterial blood pressure is practised commonly in the critically ill patient. This usually involves cannulation of the radial or dorsalis pedis artery. The hazard of bacteraemia related to an arterial cannula was described first in 1970.[1] Infection related to arterial catheterisation has received little attention in comparison with intravenous catheter related infection. Several groups have reported infection as an infrequent occurrence in the wider context of their experience with arterial cannulation, but Band and Maki[2] were the first to survey prospectively the local and systemic infective complications of arterial catheterisation, using a semiquantitative culture technique which Maki had described previously for intravenous catheter related infection.[3] They found local infection rates of 18%, and 4% developed septicaemia. Other studies that used a semiquantitative method of culture have found similar rates of colonisation and bacteraemia.[3–7] Workers who employed a simple broth technique have found a wider range of results.[8–10]

Cannulation of the radial artery complicated by abscess formation and subsequent median nerve palsy, has not been reported before and this case serves to emphasise the infective hazard associated with arterial cannulation.

Case history

A 24-year-old Caucasian male was admitted to the intensive therapy unit with a diagnosis of falciparum malaria. He had recently travelled to Nigeria and had not taken malarial chemoprophylaxis. His initial symptoms of malaise and shivering had been diagnosed as influenza.

Confusion and disorientation in time and place demonstrated evidence of cerebral involvement. His admission temperature was 39°C. Results of initial investigations were haemoglobin 9.2 g/dl, white blood cell count 10×10^9/litre, prothrombin time 19 seconds (control 13 seconds) and kaolin partial thromboplastin time 68 seconds (control 38 seconds). Arterial blood gases taken while he breathed air were

S.L. Lindsay, MB, FFARCS, R. Kerridge, MB, FFARCS, Registrars, B-J. Collett, MB, FFARCS, Consultant, Whipps Cross Hospital, Whipps Cross Road, Leytonstone, London E11 1NR.

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pH 7.38, $P\text{CO}_2$ 1.9 kPa, $P\text{O}_2$ 8.5 kPa and base deficit 11 mmol/litre. The serum Na^{2+} was 122 mmol/litre, K^+ 4.0 mmol/litre and urea 30 mmol/litre. Thick and thin films showed 15% parasitised erythrocytes with early forms of *Plasmodium falciparum*. Electrocardiogram and chest X ray were normal.

Monitoring in the intensive therapy unit included urinary output via an indwelling catheter, central venous pressure measured through an internal jugular venous cannula and direct arterial pressure measurement through a radial artery cannula connected to a continuous flushing device and a pressurised bag of heparinised 0.9% saline.

His management included an exchange transfusion of 6 units of blood, intravenous chloroquine 500 mg 12-hourly, vitamin K 10 mg daily and fresh frozen plasma. Hypoxia was treated with high inspired oxygen concentrations via a facemask.

Day 2

His confusion subsided and the parasite count decreased to 1%. He remained pyrexial. Urine output was high, with a urine: plasma osmolality ratio of 1.19 (consistent with the polyuric phase of acute tubular necrosis). His pyrexia lessened. Repeated clinical examination of his respiratory system and chest X ray remained normal. Multiple arterial blood samples taken throughout the day showed a progressive improvement in gas exchange.

Day 3

Blood, urine and throat swabs were taken for bacteriological culture because of increasing pyrexia. The site of arterial cannulation was painful when flushed, but not inflamed. Renal function deteriorated and it was decided to start peritoneal dialysis.

Day 4

The fever lessened in the early part of the day, but later increased. Continuing pain and local tenderness led to the removal of the radial cannula.

Day 5

He continued to be pyrexial and became increasingly unwell. The cannula site was inflamed, with lymphangitis, local ecchymoses and pustules. Blood cultures taken on the 3rd day grew *Staphylococcus aureus* and intravenous flucloxacillin and gentamicin were prescribed whilst sensitivity results were awaited.

Day 6

The lymphangitis diminished and the *Staphylococcus aureus* was found to be sensitive to flucloxacillin. His general condition improved, with a reduced, intermittent pyrexia.

Day 7

An abscess developed at the site of radial arterial cannulation. Thirty millilitres of pus aspirated from the area grew *Staphylococcus aureus*. The abscess was incised and drained, with debridement of the infected area. No evidence of radial artery function was found at operation. Postoperatively, it was noted that a median nerve palsy had developed, which has persisted to date.

There were no further infective complications. He was discharged to a general ward on the 8th day following admission, and went home on the 18th day.

Discussion

It is our policy to insert radial arterial cannulae using a 'no touch' technique, after the skin has been swabbed with isopropyl alcohol. Gowns, masks and gloves are not worn. The site of insertion is inspected and the entire fluid column and continuous flush device are changed every 24 hours. At the time, arterial catheter tips were not routinely cultured after removal. This code of practice is common in other centres and, in view of the complications which developed in this patient, it was thought that a review of the problems of infection in arterial lines would be appropriate.

Maki *et al.*[3] first described the use of semi-quantitative culture for the bacteriological diagnosis of catheter-related sepsis for intravenous catheters in 1977, and subsequently for arterial catheters in 1979.[2] Growth of 15 or more colonies was strongly associated with local catheter related infection and with a 15–40%

incidence of bacteraemia. The semiquantitative method of culture distinguishes infection (> 15 colonies) from contamination, and is more specific in the diagnosis of catheter related infections than broth culture.

Important features associated with infection of arterial cannulae are placement of the cannula for more than 4 days,[2,7] insertion of the cannula by surgical cutdown rather than percutaneously,[7] and local inflammation, although the absence of this sign should not be used to exclude consideration of catheter related infection.[2] Contamination is much more common when fluid lines are not changed (at least every 48 hours).[6,11] Compared with intravenous catheters, different pathogens are usually found; *Staphylococcus* spp. are the most frequently cultured, but *Enterococci*, *Klebsiella*, *Candida*, *E. coli* and other gram-negative organisms have also been identified.[6,10,12,13] Femoral artery cannulae are associated more frequently with infection than radial artery cannulae.[4,8]

Repeated blood samples are taken from critically ill patients and this involves frequent manipulation of the arterial line, which leads to an increased risk of infection.[14] Sampling requires blood to be drawn into a three-way tap, which may then act as a reservoir of infection. Strict sterility of the three-way tap is difficult to maintain in this situation.

Arterial cannulation is more difficult than venous catheterisation and the number of sites available is smaller. This may explain why rotation of the site of arterial pressure monitoring is not regular practice, although this does occur with venous cannulation.

A delay in the diagnosis of infection may occur due to lack of local signs. Arteries are generally deeper than veins and it seems that the arterial wall is less prone to inflammation. Infection in venous cannulae is introduced into a slow-moving blood channel and produces localised inflammatory changes along the vein, proximal to the cannula. During slow continuous flush through an artery, any infection spreads distally in the relatively larger area supplied by the vessel. Local signs are then related to arterial occlusion and thrombosis. Fluid may flow proximally in the artery during intermittent bolus flushing, and evidence of flush solution has been found as proximal as the subclavian artery.[15]

Guidelines[3,11,14] have been suggested for the care of arterial cannulae and pressure monitoring systems. Sterile gloves should be used for insertion. The skin should be prepared with iodine solution and, after insertion of the cannula, the use of iodophor ointment may be beneficial before a sterile dressing is applied. A percutaneous method of insertion is preferred. A record should be kept of insertion time and date and, unless there are exceptional circumstances, the cannula should be changed every 4 days. The arterial catheter, stopcock and flow valve should be considered as a sterile field and handled appropriately. Blood should not be allowed to flow back to the transducer. Site inspection and redressing should take place every 24–48 hours. Finally, the entire flushing system and reservoir should be changed every 48 hours and any cannula exposed to high-grade bacteraemia should be removed.

The arterial line and cannula should be considered as a source of infection in any unexplained bacteraemia or pyrexia. The catheter tip should be removed and cultured together with the infusion fluid, and swabs should be taken from the arterial site and sampling port.

Toxaemic patients with local purulence or inflammation should receive systemic antibiotics after the appropriate bacteriological investigations. The range of bacteria involved has been found to be different from that in venous lines,[3] and an aminoglycoside together with an appropriate anti-staphylococcal agent appears to be the best choice for empirical therapy.

The reasons for the occurrence of this very rare complication of radial artery cannulation remain uncertain. The infection could have been introduced by staff who attended to him, he may have been a staphylococcal carrier or, least probably, it may have been the result of air-borne contamination. Early detection of the abscess was difficult since fever and toxaemia characteristic of malaria were present from day 1 although, haematologically, rapid resolution occurred.

A prospective trial to evaluate local experience of infection related to arterial catheters is currently under way in this unit. We are also comparing contamination rates of fluid with time and their relationship to clinical infection. As a result of this case, our current protocol for insertion and subsequent handling of arterial cannulae is under review and, in future, it will be expected to include several of the points highlighted by this case.

Conclusion

Arterial cannulation is a useful, often vital part of monitoring the critically ill patient. It is a potential source of bacteraemia and other infective complications. Blood sampling from this site increases contamination and the risk of infection. A strict aseptic technique for insertion and sterile handling of the blood sampling port, which should then be cleared of blood after use, minimise this risk. The lack of early warning signs such as inflammation, may fail to alert the medical and nursing staff to the presence of infection. Diagnosis may also be confused if there is an initial relapsing pyrexia present. Any unexplained fever or local signs of inflammation should result in the prompt removal of the cannula, and culture of the tip and infusion fluid.

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Forum

Day-case herniotomy in children. A comparison of ilio-inguinal nerve block and wound infiltration for postoperative analgesia

M.F. Reid,* FFARCS, Registrar, R. Harris, FFARCS, P.D. Phillips, FFARCS, I. Barker, FFARCS, Senior Registrars, N.H. Pereira, FFARCS, N.R. Bennett, FFARCS, Consultants, Department of Anaesthesia, The Children's Hospital, Western Bank, Sheffield S10 2TH.

Summary

Forty-nine boys scheduled for day-case inguinal herniotomy were studied to compare ilio-inguinal nerve block and wound infiltration for postoperative analgesia. Both techniques were simple to perform and produced no complications. In the ilio-inguinal block group, 100% had either no pain or very mild discomfort when assessed 60 minutes after return to the day unit, compared to 95% in the infiltration group. Some children did appear to have pain following discharge but in all cases this responded well to simple analgesics. We conclude that both techniques provide satisfactory analgesia whilst the complications of narcotics are avoided, and suggest that simple infiltration of the wound with local anaesthetic solution should be encouraged in paediatric anaesthesia.

Key words

Anaesthesia; paediatric, outpatient.
Anaesthetic techniques, regional; ilio-inguinal block, local infiltration.

Regional analgesia is now accepted practice in paediatric anaesthesia, whereby good postoperative pain relief can be attained whilst opioid analgesics are avoided. It has a particular attraction in day-case surgery, where the early discharge of a pain-free patient with minimal systemic disturbance is possible. The topical application of local anaesthetic solution to the wound site may also have a place in paediatric anaesthesia. A comparison of intramuscular morphine, bupivacaine nerve block and topical lignocaine for circumcision in children, demonstrated topical analgesia to be the most effective, with no side effects.[1] The use of ilio-inguinal nerve block as an adjunct to general anaesthesia for ilio-inguinal herniotomy, has been popularised by some workers.[2]

The present study was carried out using either ilio-inguinal nerve block or local anaesthetic infiltration of the wound in day-case herniotomy patients, and postoperative analgesia and complications were assessed in the hospital and at home.

Method

The study was limited to boys aged between 1 and 7 years admitted to the day unit for unilateral inguinal herniotomy. All the anaesthetics were administered by one of two consultant anaesthetists. The anaesthetist assessed the child's mood on a scale of 1–5 (Table 1) during the pre-operative visit. The mood was also assessed later in the anaesthetic room immediately before induction of anaesthesia. Patient age distribution and pre-operative mood scores are shown in Table 2.

The patients were unpremedicated, in accordance with our normal practice. General anaesthesia was induced either intravenously with 2.5% thiopentone (4–6 mg/kg) or by an inhalational technique, and was maintained with oxygen, nitrous oxide and halothane breathed spontaneously. The patients were randomly allocated into two groups following induction. In the

Table 1. Mood grades.

1	Cheerful and cooperative
2	Apprehensive and cooperative
3	Tearful and cooperative
4	Uncooperative
5	Terrified and virtually unmanageable

* Present address: Department of Anaesthesia, Queens Medical Centre, Clifton Boulevard, Nottingham NG7 2UH.

Table 2. Age distribution and pre-operative mood grades: values expressed as mean (SD).

Group	Number of patients	Age, years	Admission mood grade	Induction mood grade
Ilio-inguinal	27	4.1 (1.9)	1.5 (0.7)	1.8 (1.0)
Range		1–7	1–4	1–4
Infiltration	22	3.1 (1.9)	1.7 (0.9)	2.0 (1.2)
Range		1–7	1–4	1–4

first group, ilio-inguinal and iliohypogastric nerve blocks were performed prior to surgery. Both these nerves come to lie beneath the aponeurosis of the external oblique muscle. The iliohypogastric nerve reaches this position just medial to the anterior superior iliac spine. The ilio-inguinal nerve penetrates the internal oblique muscle mediocaudally to this point to lie in the same fascial plane. A 23-gauge hypodermic needle was inserted one finger breadth medial to the anterior superior iliac spine and advanced vertically until the aponeurosis of external oblique was penetrated. Following aspiration the analgesic solution was injected at this point, and also laterally towards the iliac spine and mediocaudally towards the inguinal ligament.[3] The second group had their wound infiltrated with local anaesthetic solution following repair of the hernia. This was performed by the surgeon who infiltrated the subcutaneous layer after suture of the external oblique aponeurosis. In both groups 0.25% plain bupivacaine was used to a total dosage of 0.5 mg/kg.

Peroperatively the patients' pulse rate, respiratory rate and the presence of movement and laryngospasm were noted before and after incision, during sac traction and on closure of the wound. Duration of the procedure and time to eye opening in response to verbal command were also noted.

Once conscious, the child's pain was assessed by a senior recovery nurse using a 10-cm linear analogue scale which ranged from quiet and still, to screaming and restless. The mood grade was also noted and the child questioned about any pain. These observations were recorded at 10-minute intervals until the child was fit to return to the day unit, where a senior nurse repeated the observations at 30-minute intervals. The nursing staff were not aware of the group allocation.

A home visit was made by a district nurse on the first postoperative day and the parent completed a form that detailed the onset, nature and treatment of any pain experienced by the child since he left hospital.

Results

Peroperative measurements. Comparison of the peroperative change in respiratory and pulse rates and the incidence of movement and laryngospasm showed no statistically significant difference between the two groups. The duration of the procedure (including the anaesthetic time) and the time to recovery were also comparable; the mean times were 19.9 and 18.0 minutes respectively in the ilio-inguinal block group, and 22.7 and 16.5 minutes in the local infiltration group.

Postoperative measurements. The linear analogue pain score results are shown in Table 3. Fifty-six percent of the patients in the ilio-inguinal block group (IIB) were estimated to be completely pain free on arrival in the recovery room, and 68% had a score less than 2. Of

Table 3. Distribution of pain scores.

	Quiet and still				Screaming and restless
Pain score:	0–2.0	2.1–4.0	4.1–6.0	6.1–8.0	8.1–10
Recovery					
Arrival					
IIB ($n = 25$)	17(68%)	1	3	3	1
INF ($n = 14$)	12(86%)	1	1	0	0
Ward					
Arrival					
IIB ($n = 26$)	23(85%)	3	0	0	0
INF ($n = 21$)	15(71%)	4	1	1	0
30 minutes					
IIB ($n = 27$)	26(96%)	1	0	0	0
INF ($n = 22$)	18(82%)	2	1	1	0
60 minutes					
IIB ($n = 27$)	27(100%)	0	0	0	0
INF ($n = 22$)	21(95%)	1	0	0	0

IIB, ilio-inguinal block; INF, local infiltration. $n < 27$ (IIB) and $n < 22$ (INF) due to incomplete form filling.

those who received local infiltration (INF), 71% were pain free and 86% had a score less than 2. The majority of patients remained in recovery for less than 10 minutes. Fifty-nine percent of the nerve block group and 52% of the infiltration group were judged to be pain free on arrival in the day unit. Assessment of pain after one hour in the day unit showed 100% of the IIB group and 95% of the infiltration group to have a pain score less than 2. Statistical analysis of the pain scores using the Mann–Whitney U test showed no significant difference between the two groups. No child in either group complained of pain following 2 hours in the day unit.

Postoperative mood assessments are shown in Table 4. It can be seen that the mean mood score for each group was satisfactory (<3) both in the recovery room and the ward, and was similar to that recorded preoperatively. Vomiting occurred in seven (26%) of the nerve block group and five (23%) of the infiltration group.

Following discharge. We received 21 completed follow-up forms from each group, a response rate of 78% in the block group and 95% in the infiltration group. Seven (33%) of the former and four (19%) of the latter group reported pain since they left hospital. Pain was controlled in all cases by simple analgesia. Details of the effect of this pain on the child are shown in Table 5. All the children slept well on the first postoperative night. Of the children who did not appear to be in pain, 43% of the block group and 47% of the infiltration group received prophylactic oral analgesia. No wound complications occurred in either group.

Discussion

The use of ilio-inguinal nerve blockade for postoperative analgesia in children has been shown significantly to reduce postoperative analgesia requirements[2] and increase the number of pain-free patients.[4] The only specific complication reported with this technique was a transient femoral nerve block.[2,5] The use of intravenous morphine peroperatively has been shown to cause an increased incidence of vomiting and postoperative sedation compared with nerve block or topical analgesia.[1] All the widely used narcotic analgesics may result in an increased incidence of nausea and vomiting together with drowsiness,[6] symptoms especially undesirable for the outpatient.

Infiltration of the wound with local anaesthetic solution has been shown to improve analgesia in adults following inguinal herniorrhaphy and cholecystectomy, with no adverse effects on wound healing.[7,8] The former reference also reported good analgesia when normal saline was used to infiltrate the wound, and suggested local dilution of a pain-mediating substance. A more recent study which involved postoperative wound perfusion of subcostal incisions, showed that bupivacaine and normal saline resulted in comparable analgesia when measured by a visual analogue score but the bupivacaine group had improved forced vital capacity measurements and lower opioid requirements.[9] Bupivacaine has also been shown to have antimicrobial activity which may protect against wound infection.[10]

This study has demonstrated that good quality analgesia can be achieved following inguinal herniotomy using either ilio-inguinal nerve block or simple local infiltration of the wound. There was no clear peroperative advantage of an ilio-inguinal block prior to surgery. Wound infiltration may be advantageous in situations where skilled assistance is not available to maintain the child's airway and anaesthesia whilst an ilio-inguinal block is performed. We consider that the use of simple wound infiltration should be encouraged in paediatric anaesthesia.

Table 4. Postoperative mood assessment: values expressed as mean (SD).

Group	Recovery arrival	Ward arrival	30 minutes	1 hour	2 hours
Ilio-inguinal	2.0 (1.2)	1.9 (0.9)	1.8 (0.7)	1.3 (0.9)	1.2 (0.4)
Range	1–4	1–4	1–3	1–2	1–2
Infiltration	2.4 (1.3)	2.3 (1.1)	1.9 (0.9)	1.3 (0.5)	1.2 (0.6)
Range	1–5	1–5	1–4	1–2	1–2

For explanation of mood scale, see Table 1.

Table 5. Effect of postherniotomy pain on the child at home.

	Number who appeared to be in pain	Child cried	Child complained	Hindered movement
Ilio-inguinal ($n = 21$)	7(33%)	5	6	2
Infiltration ($n = 21$)	4(19%)	2	2	1

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Epidural catheter migration during labour

D.C. Phillips,* MB, ChB, FFARCS, Senior Registrar, R. Macdonald, PhD, FFARCS, Consultant, The Maternity Unit, Gledhow Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

Summary

A study was undertaken to determine the incidence, magnitude and direction of catheter migration in 100 patients who had epidural analgesia for pain relief in labour. Over 50% of catheters migrated from the original position at siting. The relevance of this migration and the usefulness of its measurement are discussed.

Key words

Analgesia; obstetric.
Equipment; catheter, epidural.

Epidural analgesia for pain relief in labour has been available in this maternity unit for 10 years and we now have experience of over 10 000 cases. Approximately 60% of top-ups are given by specially trained midwifery sisters. Our midwife top-ups have been relatively problem-free but there always remains anxiety about the development of either a subarachnoid block or systemic toxicity from inadvertent intravascular injection of the local anaesthetic,[1,2] due to migration of the epidural catheter. Migration of the catheter out of the epidural space into the superficial tissues of the back or through an intervertebral foramen may also occur[3] and lead to inadequate analgesia or complete failure. This frequently necessitates resiting the catheter.

We had not previously examined in detail catheter migration; the purpose of this study was to determine its incidence, magnitude and direction during labour and to see whether our management of epidural analgesia required modification.

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* Present address: D.C. Phillips, Consultant, Lincoln County Hospital.
Correspondence should be addressed to Dr R. Macdonald please.

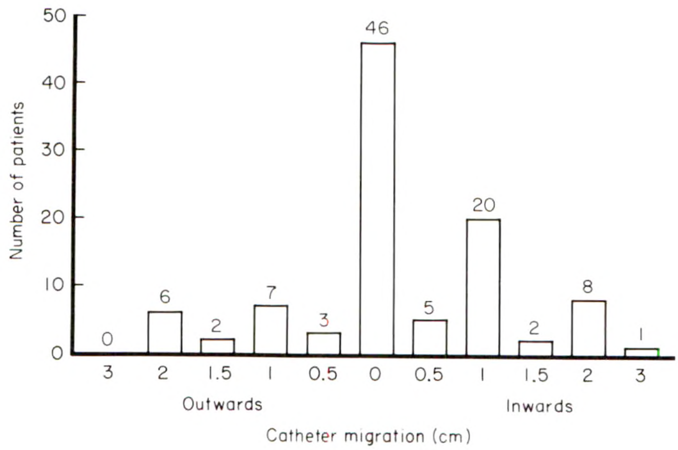

Fig. 1. Histogram showing range of catheter migration (cm).

Methods

The study was performed on 100 fit patients who requested epidural analgesia for labour. All epidural catheters were sited with the patient in the left lateral position. A record was made of the depth of the epidural space and of the length of catheter left in the space using the method outlined by Doughty.[4] The number of centimetre markings on the catheter visible from where it emerged from the skin, was also recorded; allowance was made for any skin dimpling during insertion. This was designated the skin level.

Catheters were fixed to the patient's back according to the personal preference of the individual anaesthetist but, as in most units, this usually involved looping the catheter on the skin, applying gauze, plastic spray dressing and some form of adhesive dressing such as Sleek or Elastoplast. Top-ups were given to suit each patient and a record was kept of the effectiveness of the analgesia throughout labour. The midwives were asked to record the skin level again after delivery, prior to the removal of the catheter. Any migration of the catheter could therefore be quantified and assigned a positive value if it had moved in and a negative value if it had moved out.

Results

Of the 100 epidurals, 72 were inserted at the $L_{2/3}$ and 28 at the $L_{3/4}$ interspaces. The depth from the skin to the epidural space ranged from 3–8 cm, and 2–4 cm of catheter were left in the space. The range of catheter migration is shown in Fig. 1. In 46 patients the catheter had not moved from its position at siting; in 18 it had moved outwards and in 36, inwards.

There was no significant difference in the proportion of catheters that migrated in or out when sited at either $L_{2/3}$ or $L_{3/4}$. No correlation could be found between the number of top-ups or duration of labour, and catheter migration. In none of the patients studied did the epidural cease to function because the catheter had migrated completely out of the epidural space. No correlation could be found between effectiveness of analgesia, unilateral blockade and catheter migration.

Discussion

Our experience of over 10 000 epidurals for pain relief in labour had mistakenly led us to expect that catheter migration would be in an outward direction. This was not found to be so. *Twice as many catheters migrated inwards.* This may be due to the gripping action of the ligamentum flavum which propels the catheter inwards as the patients deflex their back from the position adopted for the insertion or for other procedures. No correlation between catheter migration and analgesic effectiveness was found in this study, but significant catheter migration may occur which has a bearing on the course of epidural analgesia and its complications.

Two patients from the study are of interest. In one, where the catheter had migrated 2 cm inwards, a diagnosis of concealed dural tap was made after the occurrence of a spinal headache on the day following delivery.[5] Fortunately, this patient delivered spontaneously about one hour after the first top-up (as always, performed by the anaesthetist) and, as she had an intact perineum, no top-up was required for suturing. In the second patient, blood had appeared in the catheter at the original siting but the catheter flushed clear when it was withdrawn to leave 2 cm in the epidural space. Subsequent top-ups were uneventful until a midwifery sister gave one prior to suture of the episiotomy. The patient immediately had signs and symptoms of an intravenous injection of local anaesthetic. When the catheter was removed, not only were the terminal 3–4 cm full of blood but it had migrated 2

cm inwards, presumably into an epidural vein. These cases, and experiences such as those of Boys and Norman[6] and Park,[7] illustrate that serious complications may arise following a previously normal course of epidural analgesia.

The results of this study provide a quantitative incidence of catheter migration. Closer attention to fixation is required and we would advise adoption of the technique described by Webster[8] in obese patients and that the fixative dressing is not applied until the patient is in the position adopted for top-ups. We also plan to discontinue the use of a gauze swab at the lower end of the catheter and, instead, use a transparent adhesive dressing so that the skin level is always visible and can be inspected frequently. Should any inward migration take place, the anaesthetist should be called. We intend to modify our epidural charts to include the catheter skin level on removal, because this information may be useful in subsequent patient management.

Since 1976 we have used epidural catheters with three helical side holes. Our experiences with both the patients described here[5] lead us to believe that end orifice catheters may be safer, since one will then be sure that all the local anaesthetic emerges from the tip of the catheter wherever it is situated; thus, assessment of the test dose and first top-up is made prognostically more valuable.

There is no room for complacency in the organisation of an epidural service. Attention to detail and house audits such as this study, are necessary for the continual safety of epidural analgesia.

Acknowledgments

We are very grateful to the midwives for their assistance and to Mrs J. Rhodes for typing the manuscript.

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Anaesthesia, 1987, Volume 42, pages 664–673

Correspondence

Diamorphine stability and pharmacodynamics

Recent correspondence (*Anaesthesia* 1985; **40:** 1241; *Anaesthesia* 1986; **41:** 554–5, 1157) indicates that there is some confusion over the stability of diamorphine and disagreement about its properties in comparison with morphine. This has arisen to some extent because the lack of stability of diamorphine in solution has different consequences according to the route and mode of administration of the drug. It is, therefore, misleading to make blanket assertions.

Dr Reynolds suggests that diamorphine 'is simply a lipid-soluble and therefore quick-acting version of morphine'. This is an oversimplification. Diamorphine does have a quicker onset of action but also produces greater sedation and causes less vomiting when given intravenously, compared with morphine.[1] Diamorphine by subcutaneous or intramuscular injection, is about twice as potent as morphine.[2] These differences appear to be associated with significant amounts of diamorphine and monoacetylmorphine being detectable in the systemic circulation.[3] The greater lipid solubility of these substances compared to morphine enables rapid entry into the brain, where

All correspondence should be addressed to Dr J. N. Lunn, Editor of *Anaesthesia*, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, United Kingdom.

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they exert their effect. The active substances at the μ opioid receptor may be monoacetylmorphine and morphine but it is not possible, on the basis of present knowledge, to discount a direct contribution of the parent drug to its pharmacodynamic effects.

Dr Reynolds is also concerned about the stability of diamorphine in solution but, as Drs Hain and Kirk have pointed out, this concern is misplaced. Several studies have investigated the stability of diamorphine in solution and confirm that degradation *in vitro* to monoacetylmorphine and morphine occurs at a rate dependent upon temperature and pH.[4,5] Our own studies, a preliminary report of which[6] is mentioned by Drs Hain and Kirk, were designed to investigate the stability of diamorphine when given by continuous subcutaneous infusion. We found that in an aqueous solution that contained 1 mg/ml, at 20°C, only 2.7% degradation had occurred after 14 days and in a 250 mg/ml solution, 8.5% degradation.[7] When the experiment was repeated at 37°C, the degradation of a 1 mg/ml solution at 14 days was 13%; this demonstrates a significant influence of temperature which may be of relevance where infusion pumps are worn under clothing or kept under bedclothes. However, this is of no importance for the majority of patients in whom infusions are renewed regularly, usually every 12 or 24 hours. Significant degradation does not occur in this time. Certainly, negligible degradation is likely under the conditions described by Drs Hain and Kirk.

Solutions of diamorphine are also given by mouth and, by this route, there appears to be no difference in pharmacodynamic effects between diamorphine and morphine. This is consistent with the finding that after oral administration of diamorphine, neither the parent drug nor monoacetylmorphine is detectable in plasma.[3] Extensive first-pass metabolism takes place predominantly in the liver, so that diamorphine by mouth appears to be no more than a pro-drug for morphine. Any degradation before ingestion is likely to be irrelevant.

The lack of stability of diamorphine solutions is thus of no consequence, except possibly in the specific instance of prolonged subcutaneous infusions. Our experience is that even in this setting, infusions can be maintained for 2 weeks without renewal, with no apparent loss of potency clinically.[6]

The stability of diamorphine is not an issue when the relative merits of diamorphine and morphine are considered in different indications. Diamorphine by mouth has no advantages over morphine and may, in fact, be an inefficient way to get morphine into the systemic circulation. The far greater solubility of diamorphine makes it preferable to morphine by subcutaneous or intramuscular injection in patients who require high doses (in excess of 30 mg morphine). Diamorphine by intravenous bolus injection produces more rapid analgesia than morphine and is preferable in the treatment of severe acute pain, such as follows myocardial infarction. However, the speed of onset of analgesia is not important when continuous intravenous infusions are used, as Dr Reynolds points out, and the differences between the two drugs are minimal.

The Royal Marsden Hospital, G.W. HANKS
Downs Road, P.J. HOSKIN
Sutton, Surrey SM2 5PT V.A. WALKER

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Respiratory arrest after epidural sufentanil

This is a report of two cases of respiratory arrest after epidural sufentanil.

The first patient was a 55-year-old woman with a previous history of long-standing asthma, with few symptoms, treated with betamethasone. The second patient was a 23-year-old woman with no previous respiratory problems. No narcotics were used in premedication but both patients received sufentanil during major abdominal surgery, without complications. Postoperatively, both patients received 50 μg sufentanil in 9 ml normal saline epidurally, which gave good analgesia. Both patients had respiratory arrest after the last dose of a series: four doses of sufentanil in 20 hours in the first case, and seven doses of sufentanil in 22 hours in the second. The respiratory arrest happened within 5 minutes of the last dose of

sufentanil. No other drugs were given systemically. The patients responded well to artificial ventilation of the lungs via a facemask, and intravenous naloxone. The first patient refused any more medication so her pain cannot have been very severe. The second patient did require analgesia 1.5 hours later so the matter of reversal of analgesia by naloxone is unresolved. Both catheters were checked; neither had migrated intradurally or intravenously.

Extradural sufentanil in this dose was reported to be a good postoperative analgesic agent with no respiratory side effects.[1,2] These two cases would indicate that sufentanil 50 μg has a shorter duration of action than previously reported, and that respiratory depression can occur very rapidly after its repeated use extradurally.

Het Nederlands Kankerinstitut,
Antoni van Leeuwenkoekhuis,
Plesmanlaan 121,
1066 CX Amsterdam,
The Netherlands

C. BLACKBURN

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Spinal anaesthesia in pregnant patients

Dr Bembridge's paper on the use of hyperbaric lignocaine for Caesarean sections (*Anaesthesia* 1986; **41:** 906–9) has highlighted the problems associated with spinal anaesthesia in pregnant patients.

Some of these problems are easily corrected; for instance, their incidence of severe headache of 13% is due to the use of 25-gauge needles. Greene[1] in 1950 showed that 26-gauge needles reduce headache to 0.4% and, in our own series (unpublished) of 56 patients for Caesarean section using 26-gauge needles, only one patient (1.7%) developed a headache, which needed no active treatment.

The amount of hypotension was also worrying but previous authors[2] have shown that intravenous fluids given before the onset of block can reduce this. Ephedrine quickly corrects any hypotension and, as long as the latter is of short duration, does not adversely affect the infant.[3]

However, the problem of high blocks is not easily resolved and is probably the main reason that some anaesthetists are wary of spinal anaesthesia as a technique of regional anaesthesia for Caesarean section. Hyperbaric 5% lignocaine may have a propensity to cause this problem since Fisher[4] commented on the unexpected rapidity with which it travelled through the cerebrospinal fluid; he reported a total spinal in one patient (non-pregnant) after only 1 ml hyperbaric 5% lignocaine.

There are other reports of high block during Caesarean section in which spinal anaesthesia was associated with 3 ml plain 0.5% bupivacaine.[5] There are many reasons for these high blocks and we consider that a major contribution to them is a relative overdose in pregnant patients. We offer some evidence to substantiate this opinion.

When heavy Nupercaine was available anaesthetists were very conscious that small increases in volume could produce profound changes in the extent of the block. When it was superseded by bupivacaine 0.5%, 3 ml became almost the standard dose and it proved to be very safe. The use of the same volume in pregnant patients may have exceeded its safety margin. Standard text books state that for spinal anaesthesia, volume is the most important factor in spread; volume should be adjusted for the height of the patient and the dose of local anaesthetic should be reduced by 33–50%. Farrar and Nolte[6] stated that, on average, 0.22 ml plain 0.5% bupivacaine was needed to block one spinal segment (non-pregnant patients). Use of Nolte's guidelines and reduction of this by 50% to 0.11 ml, as recommended for pregnant patients, would mean that only 2.2 ml plain 0.5% bupivacaine could block 20 spinal segments, that is, to a level of T_2.

These facts do suggest that overdosage is one of the factors that cause high blocks in pregnant patients during spinal anaesthesia. Altering the volume of 0.5% bupivacaine we use for Caesarean section under spinal anaesthesia could go a long way to remove this problem. We should be able totally to eliminate excessively high blocks during spinal anaesthesia in pregnant patients through awareness of all the factors concerned. It is sobering to note that as long ago as 1969, Williams[7] documented 800 cases of Caesarean section under spinal anaesthesia using only 1.4–1.6 ml heavy Nupercaine without one case of high block.

Whipps Cross Hospital,
London E11 1NR

L. EDMONDSON
D.C. ERWIN

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Should ventilator alarms be compulsory?

A recent newspaper report describes the inquest on a patient who suffered irreversible brain damage after accidental, but initially unnoticed, disconnexion from the ventilator during general anaesthesia. It is easy to criticise but this distressing and often costly event can happen even to a vigilant anaesthetist if his attention is unavoidably distracted by other matters. It is also a not infrequent calamity even in an intensive care unit, despite constant nursing supervision.

The question is, so long as airway connexions retain their present primitive and unsafe design, can we today condone the use of mechanical ventilation without an alarm system in an apnoeic patient? If the answer is negative, as I believe it now must be, then the next question is what should be the mandatory characteristics of such an alarm? Few, if any, of those currently available are without fault and, of course, no piece of equipment is ever completely reliable. The medical defence organisations apparently take the view that good practice is generally determined by the consensus view of a specialty. No monitoring system can ever be a complete safeguard or diminish our obligation to be vigilant, but are we very close to the stage where the Courts may be persuaded that a failure to use an approved alarm with a ventilator is not only morally, but legally indefensible? We seem to be in the same position with regard to basic cardiovascular monitoring during general anaesthesia.

National Heart Hospital,
London W1M 8BA

A. GILSTON

A protocol for safety

The assurance of safety in anaesthetic practice is somewhat empirical and is far from objective. The editorial on the law and the practice of anaesthesia (*Anaesthesia* 1986; **41**: 1085–6) throws light on the new laws that have been promulgated by the Federal Republic of Germany on the number of tests an anaesthetist must perform on an anaesthetic machine before the day's work is started. A somewhat similar test procedure, for both routine and emergency work, was also suggested here.[1] We might make some progress if a standard protocol for safety were adopted by anaesthetists.

Here are a few suggestions about such a protocol. It should be made mandatory that anaesthetists perform appropriate tests on the anaesthetic machine. A proforma (similar to that used by garage mechanics) should be completed and include the anaesthetist's name, designation, date, time and the identification of the operating theatre. The most senior anaesthetist should countersign.

It would now perhaps be justified to accord the correct 'status of responsibility' to the work done by paramedical staff, such as operating department assistants (ODAs), engineers and/or technicians who maintain equipment in hospital. The proforma should be clearly divided in the areas according to the department that performed the tests (anaesthetist, ODA, hospital engineer and/or technician). Suction apparatus, for example, is usually assembled by the ODA in the operating room before every operation. Completion of this part of the protocol could be a matter of pride, responsibility and professional satisfaction for an ODA.

This protocol and proforma would, firstly, force anaesthetists to acknowledge that important work is done by the paramedical staff. Secondly, the paramedicals would be answerable for their own work and anaesthetists would be free from the burdens of vicarious responsibility. Proper records of maintenance work are already required by HEI 98. Adherence to such a protocol would demand an extra amount of time to be spent by all concerned and this would need to be noted by the Health Authorities.

A protocol like this might be viewed as a deterrent to their normal working practice by those who do not wish to be accountable for their work, whereas, for conscientious workers who are not overwhelmed by imaginary fears, a protocol for safely would act as a gentle reminder of a rigid discipline which needs to be followed to ensure the safety of patients.

King George Hospital,
Ilford, Essex IG2 79R

G.N. KALLA

Reference

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Nitrous oxide does not alter oxyhaemoglobin dissociation in dog or man

We read with interest the recent article by Shah *et al.* (*Anaesthesia* 1986; **41:** 586–8). They reported that the mean P_{50} of human blood equilibrated with nitrogen (70%), carbon dioxide (5%) and oxygen (25%) was not significantly different from the mean P_{50} of blood equilibrated with nitrous oxide (70%), carbon dioxide (5%) and oxygen (25%). At the time this article was published, we also were examining the effects of nitrous oxide (50%) on the P_{50} of blood. We examined both human and canine blood because alteration of P_{50} by nitrous oxide would affect both our clinical practice and our laboratory work in dogs. Our results in six human volunteers and six dogs agree with those of Shah *et al.* In our studies the P_{50} of human blood was 3.418 kPa (SD 0.293) and the P_{50} of canine blood was 3.764 (kPa (SD 0.372) in the absence of nitrous oxide, similar to previously reported values. P_{50} values measured in the presence of nitrous oxide (50%) were 3.644 kPa (SD 0.146) for human blood and 3.937 kPa (SD 0.146) for canine blood. For both human and canine blood P_{50} values in the presence of nitrous oxide were not significantly different from P_{50} values in the absence of nitrous oxide.

University of Washington School of Medicine, Seattle, WA 98195, USA

K.M. Powers
A.A. Artru

Bowel sounds during artificial ventilation

We agree with the observation by Shelly and Church (*Anaesthesia* 1987; **42:** 207–9) that bowel sounds are a poor indication of when to start enteral nutrition in patients who receive artificial ventilation of the lungs. We have observed this phenomenon in five patients in the past 6 months: one with a head injury, two with pneumonia and two after abdominal aortic aneurysmectomy. Midazolam and opiates were used for sedation and analgesia but only the patient with the head injury received neuromuscular blocking agents.

It is routine practice in this ICU to leave nasogastric tubes on free drainage and to aspirate them every 6 hours. In these five patients without bowel sounds there was no free drainage of gastric contents and the 6-hourly aspirations yielded less than 40 ml. Enteral feeding was commenced using water, which was changed to a proprietary feed after 24 hours. Feeding was stopped for one hour every 6 hours, followed by aspiration of the nasogastric tube. The absence of bowel sounds was confirmed by at least four observers but all patients absorbed their feed with minimal gastric contents obtained at the 6-hourly aspirations. The injection of 100 ml air down the nasogastric tube at hourly intervals did not result in the return of bowel sounds.

Air swallowing appears not to occur in some patients during artificial ventilation even when neuromuscular blocking agents are not used. This phenomenon demonstrates the need in critically ill patients, for nasogastric tubes of sufficient bore to allow aspiration of stomach contents; fine bore feeding tubes are inadequate for this purpose.

The Intensive Care Unit, Addenbrooke's Hospital, Hill's Road, Cambridge CB2 2QQ

A.R. Manara
W. Kinnear
G.R. Park

Prolonged haemodynamic disturbance following attempted retrobulbar block

We wish to report the occurrence of prolonged haemodynamic disturbance following a retrobulbar block in a 54-year-old female who suffered from bilateral closed-angle glaucoma.

Two ml 3% lignocaine were injected into the retrobulbar space using a blunt 4-cm needle after sedative premedication. Approximately 5 minutes later a large orbital haematoma developed accompanied by the sudden onset of severe hypotension and bradycardia. Cardiac standstill rapidly ensued and resuscitative measures were instituted immediately. An infusion of adrenaline was started which quickly restored systolic arterial blood pressure to about 200 mmHg but the heart rate remained less than 50 beats/minute. After about half an hour it was possible to extubate the patient, who was then conscious, but the need for inotropic support and anticholinergic intervention remained for about 20 hours. Two weeks after the incident the patient underwent uneventful surgery under a general anaesthetic. We believe this to be the first report of prolonged haemodynamic disturbance following attempted retrobulbar block. The need for repeated doses of anticholinergic agent to maintain heart rate suggests to us that this might be a manifestation of a persistent oculocardiac reflex.

University Hospital, Cluj Napoca, Romania

E. Cardan
R. Pop
S. Negrutiu

Hypotensive anaesthesia for middle ear surgery

The paper on this subject (*Anaesthesia* 1986; **41**: 637–40) requires some comment.

Firstly, the means and the ranges of the respective doses of labetalol in the two groups, were described in the article but only the means of the intra-operative blood gas analysis values were published. The average $P\text{aCO}_2$ was 8.2 kPa and the average pH, 7.22 for each group; the ranges obtained of these estimations would interest all readers. Kerr[1] used pentolinium, nitrous oxide, halothane, a Ruben expiratory valve and somewhat lower arterial pressures, and reported very high $P\text{aCO}_2$ values in some of the patients in this series.

Secondly, they described the use of labetalol in 10 mg increments intravenously and, in the manufacturer's advertisements, up to 20 mg intravenously appears to be recommended. Possibly my patients are different because the drug is used occasionally in gynaecological surgery, to counteract hypertension in treated or untreated hypertensive or normal patients, with a muscle relaxant technique that uses nitrous oxide and 0.5% halothane. After several episodes of transient dysrhythmias and hypotension after 5 mg intravenously, I now use 2.5 mg increments. Colleagues have similar experience after rapid injections. Bradycardia may also require treatment.

University of Natal,
P.O. Box 17039,
Congella 4013,
South Africa

R. WILLIAMSON

Reference

1. KERR AR. Anaesthesia with profound hypotension for middle ear surgery. *British Journal of Anaesthesia* 1977; **49**: 447–51.

A reply

Thank you for the opportunity to reply to this letter. The range of values for pH was 7.34–7.07 in the halothane group and 7.37–7.14 in the isoflurane group. The range of $P\text{aCO}_2$ was 6.42–11.00 kPa in the halothane group and 6.35–10.43 kPa in the isoflurane group, which confirms the high values found by Kerr, in some patients.

In reply to the second point, our preliminary studies indicated that 10 mg increments of labetalol were suitable to provide the desired level of hypotension. However, it must be stressed that this dosage was given in very different circumstances to those described in Dr Williamson's letter. All the patients in our study were healthy (ASA grade 1) and, thus, no patient with treated or untreated hypertension was included. Ventilation was spontaneous and, although this is controversial as part of a hypotensive technique, it is more likely to ensure maintenance of cardiac output. Furthermore, the initial dose of labetalol was administered soon after induction of anaesthesia, before surgery began, and the concentrations of halothane and isoflurane in the anaesthetic system were strictly controlled because of the synergistic effect of labetalol and the volatile agents. The concentrations of the halogenated anaesthetic agents were measured by the Engström Emma and the blood pressure measured directly following arterial cannulation. Labetalol and halothane result in a bradycardia but this was not a problem in our series, possibly because our patients were a relatively young group. Bradycardia has been found to be more of a problem in patients over 50 years of age.[1]

We agree that a 10 mg bolus of labetalol might cause an undesirable decrease in blood pressure or severe bradycardia under some circumstances but we have found it to be ideal as part of an anaesthetic technique designed to produce deliberate hypotension and good operative conditions for middle ear surgery.

Gloucestershire Royal Hospital,
Great Western Road,
Gloucester GL1 3NW

R.J. ELTRINGHAM
M.L. FAIRBAIRN

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Atriobronchial fistula: an unusual complication of intravenous feeding in the presence of a mediastinal abscess

This interesting problem was encountered in a 71-year-old, previously fit woman who presented for a cataract operation at another hospital.

Tracheal intubation proved impossible because there was a receding jaw and cervical spine disease. The operation proceeded while the patient breathed spontaneously from a Bain system connected to a nasal airway. Anaesthesia was maintained with nitrous oxide and halothane.

Postoperatively she developed surgical emphysema of the neck and face, hoarse voice and dysphagia. A tentative diagnosis of perforated larynx was made and she was treated expectantly. She discharged herself, against medical advice, one week postoperatively when the surgical emphysema showed improvement.

Eleven days later she presented to our hospital in a toxic, delerious state. Blood cultures grew *Streptococcus Millerii* and *Klebsiella*. A chest X ray showed

patchy consolidation in the right paratracheal area with small collections of air consistent with a mediastinal abscess. A barium swallow showed a tear in the upper oesophagus with extravasation of contrast medium on the right side towards the mediastinal abscess. A tunnelled 14-G Vygon Nutricath was inserted into the right subclavian vein under local anaesthesia and, after some adjustment, the tip was shown to be in the low superior vena cava. Intravenous feeding was commenced.

Nine days later the patient rapidly deteriorated overnight and began to cough creamy thick sputum, which was noted by the nursing staff to look like the parenteral nutrition fluid. A chest X ray showed patchy infiltration throughout the right lung. A Minitrach was inserted. Injection of methylene blue into the central feeding line resulted in coughing and the appearance of methylene blue from the tracheostomy. Blood could still be aspirated from the central line but the patient did not experience haemoptysis. Radio-opaque contrast was injected into the central line under image intensifier control. Some of the dye passed into the right atrium but the remainder entered the right main bronchus at the level of the lower lobe division. There was no extravasation of the fluid into the mediastinum after injection of contrast into the Minitrach. A small amount of contrast entered the right atrium. The trachea and main bronchus were patent and otherwise normal in appearance. The feeding line was removed and the patient fed via a gastrostomy. Inspection of the feeding line revealed no abnormality.

Another 14-G Vygon Nutricath was inserted into the left subclavian vein 6 weeks later when the patient's condition deteriorated again. This again had the tip in the superior vena cava and was left for one week without problems. The abscess was eventually drained through a paraspinal approach (intubation was uneventful this time). It was found to be on the right posterolateral aspect of the trachea, the cartilages of which were palpable, and contained about 200 ml pus which grew mixed bowel organisms. Her postoperative course was good, apart from pseudomembranous colitis, and she was eventually discharged home.

The problems of iatrogenic oesophageal perforation were recently reviewed;[1] however, a literature search has failed to reveal any previous reports of an atriobronchial fistula. The superior vena cava lies directly anterior to the root of the right main bronchus but, more laterally, the pulmonary vessels are the closest structures. The azygos vein arches over the right hilum.[2] The abscess was found on the right posterolateral aspect of the trachea and this situation would favour communication between the azygos vein and the bronchus rather than the more anterior superior vena cava, although the anterior extent of the abscess was not defined and radiologically it seemed to communicate with the right atrium. Indeed, it is difficult to explain the fact that while a fistula between the right atrium and right main bronchus was demonstrated radiologically, the patient experienced no haemoptysis. Presumably the catheter had created a valve between the atrium and the bronchus.

Perhaps there is a case for siting the tip of feeding catheters in vessels other than the superior vena cava or right atrium in cases of mediastinal infection.

Kingston Hospital, P.J. GRAZIOTTI
Kingston-upon-Thames KT2 7QB

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Beta blockade, suxamethonium and potassium

We were interested to see the article by Maryniak *et al.* (*Anaesthesia* 1987; **42:** 71–4) which examined the effect of beta blockade on the release of potassium after suxamethonium. Their study, as the authors admit, was confined to a period of 6 minutes after suxamethonium was administered and did not examine the possibility that beta blockade may prolong the increase in potassium. Evidence suggests that a beta-adrenoreceptor blockade impairs the extrarenal uptake of potassium[1] and, in a suitably blocked patient, the potassium released after suxamethonium is therefore prevented from re-entering the cells. The mechanism appears to be β_2-mediated.[2] In this case we would expect to see not an early increase in potassium but, possibly, a prolongation of the period of elevated potassium after suxamethonium.

We have shown in a study in dogs, partly presented in abstract form[3] and shortly to be published in full,[4] that acute beta blockade alters the time to peak increase in potassium after suxamethonium but does not increase peak levels. The peak increase in potassium in controls was at 3 minutes and in the beta-blocked animals, at 30 minutes. The full effect of beta blockade on the release of potassium after suxamethonium in man has still to be elucidated.

The Hospital for Sick Children, D.R. GOLDHILL
Great Ormond Street,
London WC1
Massachusetts General Hospital, J.A.J. MARTYN
Boston, MA 02114, USA

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A hazard of free-standing vaporizers

It has been established that Selectatec vaporizers attached to the back bar of an anaesthetic machine are, when improperly secured, a potential site for leakage of anaesthetic gases from the patient system. This is not a problem when free-standing vaporizers are used, since male/female connexions allow insertion of the vaporizer into the system without the necessity for a locking mechanism.

We should like to report a case in which the use of a free-standing isoflurane vaporizer (Cyprane Mark 3) was associated with leakage of anaesthetic gases, secondary to a defect in the outlet connector. This potential hazard is, to our knowledge, hitherto unreported.

A 16-year-old boy was anaesthetised for routine four-vessel cerebral angiography. After induction and tracheal intubation his lungs were ventilated with nitrous oxide (4 litres/minute) and oxygen (2 litres/minute) using a Manley Pulmovent. Isoflurane 0.75% was administered via a free-standing Cyprane Mark 3 vaporizer. A persistent gas leak was heard although an adequate tidal volume was delivered. The connectors within the system were all found to be secure and there was no apparent leakage from the anaesthetic tubing. The fault was thought to lie in the vaporizer which was added to the system after induction and

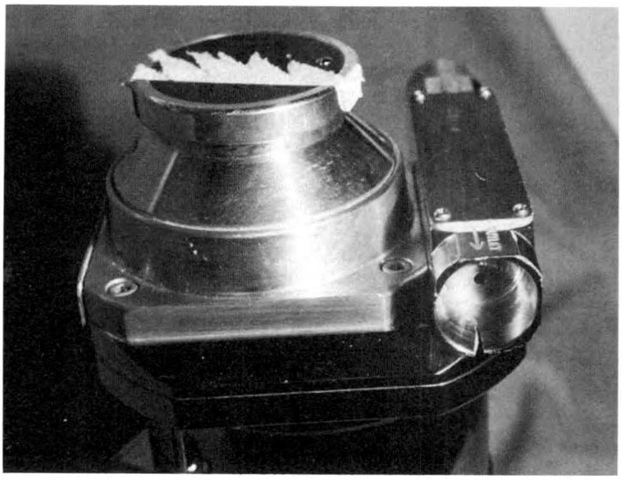

Fig. 1.

tracheal intubation. The leak disappeared after the vaporizer was removed. On close inspection a serious defect was demonstrable in the female outlet of the vaporizer (Fig. 1). This crack may have occurred as a result of excessive leverage by the male connector within the female outlet. It would also seem likely that the outlet connexion had been weakened previously either by careless handling or due to a structural fault in manufacture.

This leak was detected almost immediately but one could imagine that in a noisy operating room such a leak might have gone unnoticed, with the subsequent risk of inadequate patient ventilation and all its consequences.

Atkinson Morley's Hospital,
Wimbledon,
London SW20 0NE

J.P. Van Besouw
A.C. Thurlow

Modification of Macintosh laryngoscope for difficult intubation

Moderate difficulty at tracheal intubation can frequently be overcome by simple measures rather than by resort to techniques such as fibreoptic endoscopy, awake intubation or retrograde cannulation. We have recently used a modified Macintosh laryngoscope blade in a series of patients and feel it is a significant

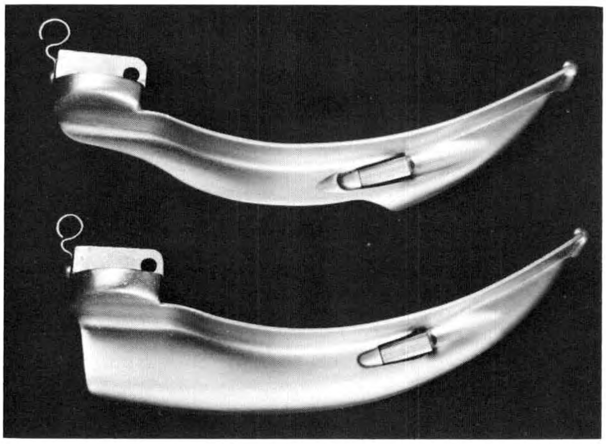

Fig. 1.

improvement over the standard blade in many of these cases.

The modification (Fig. 1), carried out by our Medical Physics Department, consists of a reduction in the height of the flange at the hilt of the blade but with no alteration to the position of the light source. The reduction in the profile of the blade allows more than one centimetre additional movement of the laryngoscope when the attempt to align the mouth, pharynx and larynx is made; it is, therefore, extremely useful in patients with limited mouth opening. There is, in addition, a decreased risk of damage to prominent upper teeth.

We consider that this simple modification to a standard piece of anaesthetic equipment has been a great help in our everyday practice and we are at present in discussion with Penlon Ltd of Abingdon, about commercial manufacture.

Morriston Hospital,
Swansea SA6 6NC

C.C. CALLANDER
J. THOMAS

Fixation of epidural catheters

One of the causes of failed obstetric epidural analgesia is the accidental withdrawal of the catheter from the extradural space. This is more likely to occur if insufficient attention is paid to securing the catheter after its insertion.

We have developed, after a series of such events, an inexpensive, simple and effective technique which other readers may find beneficial in reducing the incidence of this problem. Once the area of skin that surrounds the catheter exit site is dry and free from blood it is sprayed with a plastic dressing. When sticky, a small, circular adhesive plaster (Band-Aid) is applied and the plaster crimped around the catheter as illustrated (Fig. 1). This ensures fixation of the catheter to the plaster which is adherent to the skin. After this it can be fixed in the more usual manner.

This technique was started 6 months ago and now this problem does not happen at our hospital.

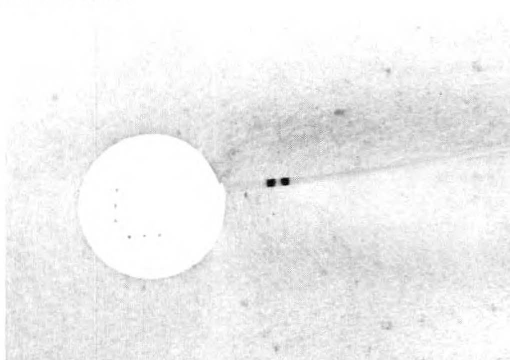

Fig. 1.

Whipps Cross Hospital,
London E11 1NR

D.G. MASON
L. EDMONDSON
P. MCHUGH

Humidifier-induced hypercarbia

Recently a Siemens humidifier (153) was used on a patient who weighed 11 kg. The manufacturers state that the apparatus deadspace is 70 ml which must be allowed for when ventilation variables are adjusted. Despite an increase in imposed ventilation the end tidal carbon dioxide increased by 1 to 1.5% and the

peak airway pressure increased from 1.5 to 3.0 kPa. We also used the device again in a 20-kg patient; this confirmed the above experience.

The manufacturer states that the humidifier can be used in the tidal volume range of 100–1500 ml. The increase of tidal volume, from 110 to 180 ml in the first case above, might have detrimental cardiovascular effect although it might not be significant in patients with larger tidal volumes. The package insert mentions an increase in ventilation and does not emphasise that this refers to *tidal* ventilation; since one adjusts minute ventilation with the Siemens ventilator this may confuse the unwary. Perhaps the device should be avoided when the tidal volume is less than 400 ml.

Cook County Hospital,
Chicago,
IL 60612-9985, USA

R. RAJU

A reply

It may very well be the case that an increase of the tidal volume with the size of the deadspace volume will not be sufficient to achieve the desired end tidal carbon dioxide concentration. This is due to the fact that compensation for deadspace is not a static procedure. An added deadspace at small tidal volumes may induce a relatively high increase of the F_{ICO_2} in the inspired gas. This will be mirrored in an increased $F_{E'CO_2}$ if compensation is achieved by an increase in V_T equal to the added deadspace. In this situation an additional increase of V_T would be needed, together with other ventilator adjustments to decrease the airway pressure.

We think the recommendations for use printed on the package are adequate. Clinical and physiological aspects depend on the individual patient and the way the product is used must be considered and decided upon by the clinician.

We would also like to point out that Siemens manufactures two other HME-type humidifiers with smaller deadspace volumes; the SH 152 has approximately 55 ml deadspace and the SH 151, approximately 30 ml deadspace.

Siemens-Elema AB,
S-17195 Solna,
Sweden

S.-G. OLSSON

Beating the blocked balloon

A 44-year-old female alcoholic was admitted for elective injection of oesophageal varices but coincidentally bled from them before treatment.

Treatment with a Sengstaken tube on traction was successful but when removal of the tube was attempted, it proved impossible to aspirate the gastric balloon although radiography confirmed that it was still inflated. Consideration was given to three options: endoscopic rupture of the balloon, ultrasound-guided percutaneous rupture and clearance of the balloon channel. Water injection was ineffective and so a 150-cm, Teflon-coated angiographic catheter guidewire was obtained. This slid smoothly down the water channel and stopped with an obvious sensation when it touched the distal end of the balloon. Aspiration of 300 ml of somewhat turbulent fluid was then easily accomplished.

This technique could be applied to any balloon-tipped device (most obviously bladder catheters) and has the advantage of being a safe, non invasive procedure which I would commend to your readers.

14 Brittens Close,
Guildford,
Surrey GU2 6RJ

R.L. COTTINGHAM

Anaesthesia, 1987, Volume 42, pages 674–681

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The collator of this section is Dr L. Kaufman, MD, FFARCS, Anaesthetic Office, The Rayne Institute, University College, University Street, London WC1E 6JJ. Dr Kaufman is prepared to provide on request, and at a modest charge, a new additional service to our readers. References from January 1984 have been entered on data base. The data are held on Dbase II, cpm 86 and on DBase III, MS Dos and are available on disc, together with a program providing search facilties. Enquiries direct to Dr Kaufman at the above address please.

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Corporate author

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. *Scandinavian Journal of Clinical Laboratory Investigation* 1976; **36:** 119–25.

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BOOKS AND OTHER MONOGRAPHS

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OSLER AG. *Complement: mechanisms and functions.* New York: Prentice-Hall, 1976.

Corporate authors

American Medical Association Department of Drugs. AMA drug evaluations, 3rd edn. New York: Publishing Sciences Group, 1977.

Editor, compiler, chairman as author

RHODES AJ, VAN ROOYEN CE, *comps. Textbook of virology: for students and practitioners of medicine and other health sciences,* 5th edn. Baltimore: The Williams & Wilkins Co., 1968.

Chapter in book

WEINSTEIN L, SWARTZ MN. Pathogenic properties of invading micro-organisms. In: SODEMAN WA Jr, SODEMAN WA, eds. *Pathologic physiology: mechanisms of disease.* Philadelphia: W.B. Saunders, 1974: 457–72.

Agency publication

National Center for Health Statistics. Acute conditions: incidence and associated disability, United States, July 1968—June 1969. Rockville, MD: National Center for Health Statistics, 1972. (*Vital and health statistics, Series* **10:** Data from the National Health Survey, No. 69) [DHEW publication No. (HSM) 72–1036].

OTHER ARTICLES

Newspaper article

SHAFFER RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help to cure alcoholism and insomnia, explain mental illness. How the messengers work. *Wall Street Journal* 1977 Aug 12: 1(col 1), 10(col 1).

Magazine article

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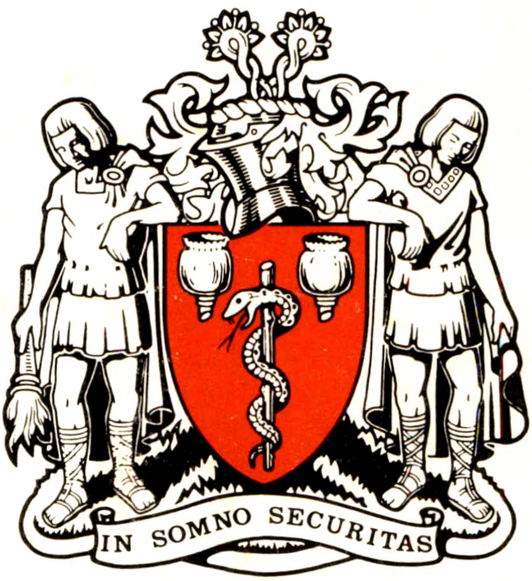

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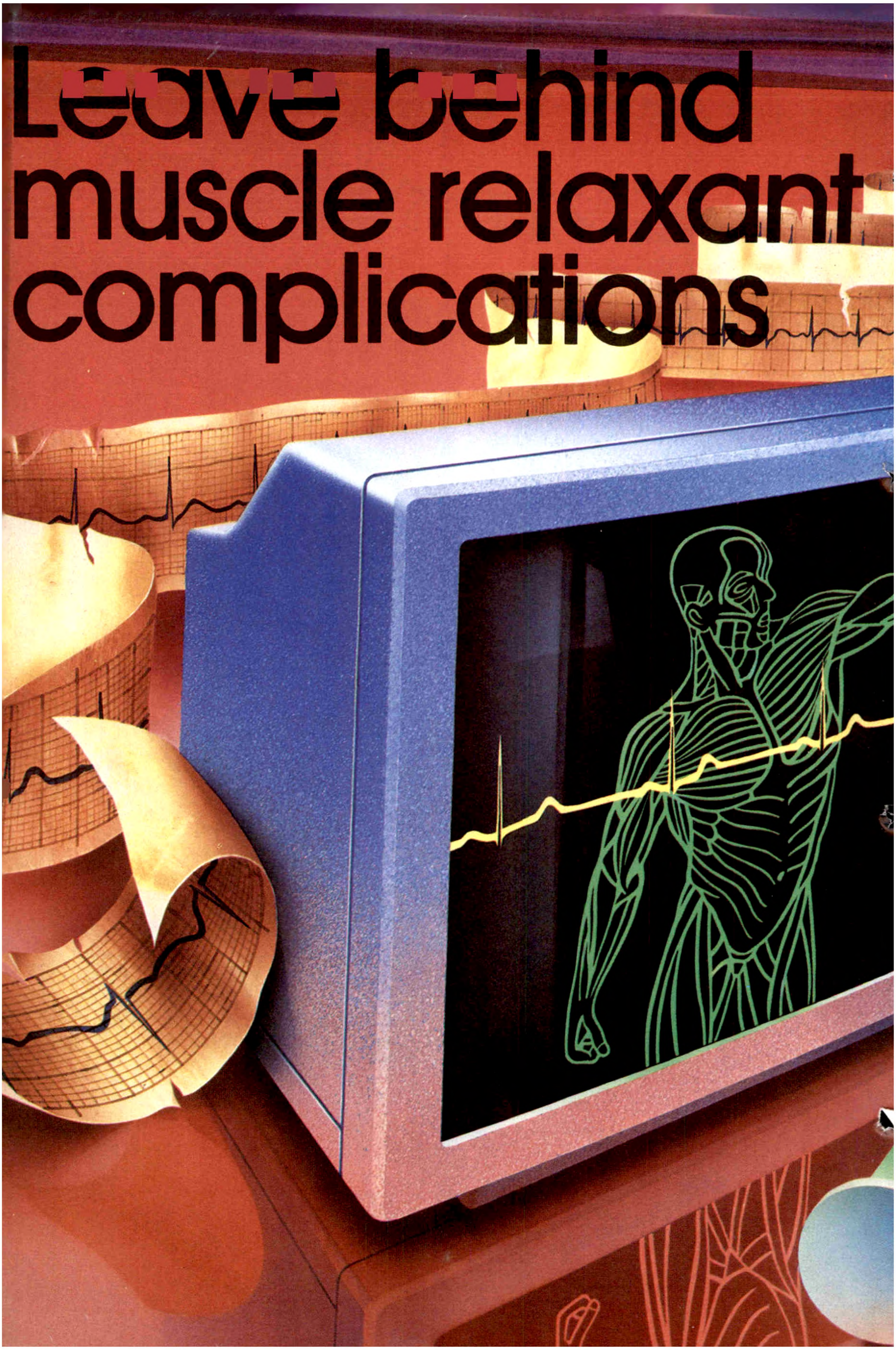
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Anaesthesia, 1987, Volume 42, pages 683–684

Editorial

Minimal monitoring and vigilance *

'Was there any question of malfunction of the electrocardiograph?' was a question at a Coroner's enquiry about an operative death.

The question underlines a feeling many anaesthetists have about basic or minimal monitoring by machine. The questioner assumed that an electrocardiograph (ECG) was attached to every patient: this may have been a considerable assumption. It was not at all clear whether an ECG was attached at the moment of arrest; indeed, the answer could have been given truthfully without confirmation or denial, for undoubtedly it was subsequently in use and worked properly.

A seminar on this topic was held recently at 9 Bedford Square. A group of Linkmen met to discuss the question of minimal monitoring. There seemed to be a measure of agreement, despite natural differences of opinion, that there already exists in practice, an accepted norm for the basic minimum of mechanical and electrical monitoring of the anaesthetised patient.

Every patient should, in the writers' view, be attached to an ECG monitor and the anaesthetist should be provided with a device to measure the heart rate and blood pressure. Some means of monitoring ventilation should be present, whether by direct auscultation, by visual assessment of a reservoir bag or by use of a respirometer. Stethoscopy, precordial or oesophageal, is commonly used in children but, surprisingly to some, not in adults. These simple measures can provide most of the information which can be obtained by the most esoteric equipment available.

Two considerations weigh against the use of even these elementary means in every case. Firstly, how does one reconcile these ideals against the widespread practice in the United Kingdom of induction of anaesthesia in anaesthetic (induction) rooms? It could be reasoned that if induction of anaesthesia is the most critical time then monitoring, if it is to be done at all, should be during this period. Nevertheless, everyone understands that maintenance and recovery are also hazardous, particularly when maintenance of anaesthesia can last such a long time. To state that monitoring should start at or before induction is not to say that it should be neglected later. Secondly, is it either likely or realistic in practical terms, for monitoring to be deployed when the procedure is very brief? Anaesthetists all know that brevity does not necessarily mean safety.

Both these objections are answered relatively easily. New developments in microelectronics and the widespread application of microprocessors have enabled automatic monitoring systems to achieve high reliability and this has been reflected in their wide acceptance and use. The measurement of blood pressure by automated oscillotonometric techniques is commonplace and many anaesthetists have now come to regard this as the standard method; and by standard, they seem to imply that the devices should be available everywhere.

The safe monitoring of artificial ventilation remains an area of concern. It is unsatisfactory that, at present, ventilators can still be designed without disconnexion alarms as integral features. There can be few anaesthetists who have not noted a disconnexion of the patient from the ventilator at some time, and few others who have not cause to thank a timely alarm which has drawn their attention to it. It seems merely prudent that one should have the assistance of electronic vigilance to guard against this life-threatening hazard.

Furthermore, it is surely reasonable to be certain that the delivered gas contains an adequate concentration of oxygen and that the delivery device should display that concentration continuously. The argument is sometimes advanced that nothing more than flowmeters is required but the avail-

* This editorial is loosely based on discussions at a seminar for Linkmen held at 9 Bedford Square in February 1987.

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ability of independent analysis of concentration, with alarms, seems to be an advance which should not be gainsaid. If a device is available, then is it not reasonable for it to be used?

All the foregoing apply to the assessment of the delivery of adequate amounts of oxygen to the peripheral tissues of the body by way of the circulation. There now exists a single method of monitoring which appears to combine the virtues of many monitors: the pulse oximeter. The cost of these devices may seem at the moment to be prohibitive and their widespread acceptance appears to be limited by economic constraints. It may be argued that if the cost of a pulse oximeter were to be shared by the number of cases that go through each anaesthetic delivery point annually, then the real cost of improved vigilance for each case would be reduced to single figures. Averaged over a suite of operating rooms this is a trivial sum but, in terms of one medicolegal settlement of a hundredfold that figure, it is cheap. Representatives of defence organisations at the seminar emphasised that employing authorities had a responsibility to provide appropriate facilities and, if on request these were not provided, then there might be a case to answer in the event of a claim against them.

We are all aware of the shortcomings of electronic systems but we should not be too complacent about our need for reliable backup to human vigilance and improved training. Anaesthetists should therefore advise their employing authorities on what they consider to be the basic minimum for monitoring apparatus to be provided at every anaesthetising location. Patients expect, and deserve, at least this.

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Editorial notices

Anaesthesia News

Copy for *Anaesthesia News* should be sent to the Editor as and when it becomes available. It is hoped that publication will occur within 3 months of receipt.

Submission of manuscripts

Manuscripts must be submitted in accordance with the internationally recognised *Uniform requirements for manuscripts submitted to biomedical journals* (*British Medical Journal* 1979; **1:** 532–5). Details will be found in the Notice to Contributors to *Anaesthesia* at the end of this issue.

Anaesthesia, 1987, Volume 42, pages 685–689

Serum fluoride levels in morbidly obese patients: enflurane compared with isoflurane anaesthesia

P. J. STRUBE, G. H. HULANDS AND M. J. HALSEY

Summary

Obese patients are known to metabolise anaesthetic agents more than patients of normal weight. The extent of this was investigated by the measurement of serum fluoride concentrations in 10 morbidly obese patients undergoing gastroplasty. Five were allocated to receive enflurane and five to receive isoflurane supplemented anaesthesia. The mean peak serum fluoride concentrations after enflurane anaesthesia were greater (22.7 μmol/litre, SE 2.9) than after isoflurane anaesthesia (6.5 μmol/litre, SE 0.6). The mechanisms and implications of this finding are discussed.

Key words

Complications; obesity.
Metabolism; anaesthetics.

The morbidly obese represent a high risk group for toxicity due to biodegradation of anaesthetic agents to reactive intermediates or toxic products, such as fluoride ions. Renal toxicity increases as peak serum inorganic fluoride levels increase above 50 μmol/litre,[1] and subclinical nephrotoxicity has been reported at lower levels maintained for prolonged periods.[2] However, obese patients are found to metabolise certain anaesthetic agents to a greater extent than subjects of normal weight.[3–6] Peak serum fluoride levels are higher in obese patients during enflurane anaesthesia[4] and increase at twice the rate found in patients of normal weight. Isoflurane is associated with the lowest degree of biotransformation of all the fluorinated hydrocarbon anaesthetics.[7] However, previous human studies relating to isoflurane metabolism have been confined to subjects of normal weight.[8–10] The present study was therefore designed to assess the degree of biodegradation of isoflurane to free fluoride in morbidly obese patients. These data are compared with those from a concurrent control group of patients who received enflurane.

Methods

Ten morbidly obese female patients were studied (Table 1). All were scheduled to have vertical banded gastroplasty performed for failure to lose weight by ordinary means. None was a smoker, drug taker or alcohol abuser. Ethical approval and informed consent were obtained.

P.J. Strube,* FFARCS, Senior Registrar, G.H. Hulands, FFARCS, Consultant, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, M.J. Halsey, MA, DPhil, Head of HPNS Group, Division of Anaesthesia, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

*Present appointment: Consultant, Wycombe General Hospital, Queen Alexandra Road, High Wycombe, Bucks. HP11 2TT.

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Table 1. Patient data. Values expressed as mean (SE).

	Enflurane (n = 5)	Isoflurane (n = 5)
Age, years	39.2 (4.6)	31.0 (3.9)
Weight, kg	121.2 (9.4)	120.4 (7.6)
Height, cm	163.0 (3.0)	166.8 (4.5)
BMI,* kg/sq. m	45.6 (5.3)	43.3 (2.1)
FRC, litres	2.5 (0.6)	1.8 (0.2)
$Pa\text{O}_2$†, kPa	12.3 (0.8)	12.0 (0.3)
Dose, MAC hours	2.3 (0.2)	2.5 (0.3)

* Body weight/height^2.
† On air, seated.

Table 2. Lung function.

Patient	Vital capacity (litres)	Functional residual capacity (litres)	$Pa\text{O}_2$ *(kPa)
1	4.6	2.1	11.3
2	4.1	1.5	12.6
3	3.5	1.3	12.5
4	4.7	1.8	12.3
5	3.2	2.2	11.5
6	3.0	1.6	13.2
7	3.0	4.3†	9.5
8	2.4	1.5	11.9
9	4.7	2.6	12.6
10	3.5	2.3	14.3

* On air, seated.
† Asthmatic patient.

Five were randomly allocated to be anaesthetised with isoflurane and five with enflurane. Pre-operative screening included lung volumes, functional residual capacity and arterial blood gases (Table 2). Serum electrolytes, creatinine and liver function were all within normal limits. All patients were premedicated with papaveretum 20 mg and atropine 0.6 mg. After pre-oxygenation, anaesthesia was induced with sodium thiopentone (300–400 mg) followed by suxamethonium 100 mg for tracheal intubation along with application of cricoid pressure. Morphine 5–10 mg was given at induction of anaesthesia. Ventilation continued with nitrous oxide and oxygen until central venous access was secured via the right internal jugular vein. Blood was sampled and anaesthesia continued with either enflurane or isoflurane (1.0 MAC) in 50% oxygen and nitrous oxide. Pancuronium bromide 8 mg was used for muscle relaxation. Sufficient drug doses were given at the start to avoid the need for increments. The radial artery was cannulated for serial blood gas analysis and ventilation controlled to maintain normocapnia. Arterial oxygen tension remained above 10 kPa. End tidal concentrations of isoflurane and enflurane were measured with a Datex Normac analyser (rate less than 15 breaths/minute) and MAC hours of enflurane and isoflurane calculated. The duration of surgery was from 2 to 3 hours. Blood samples were collected before administration of isoflurane or enflurane and at intervals for 48 hours postinduction. The serum was separated, frozen and ionic fluoride concentration determined by direct ion-specific potentiometry using a fluoride electrode. The sensitivity of the method was 0.5 μmol/litre. Care was taken to avoid any fluoride contamination from the water or glassware. Serum urea, creatinine and electrolytes were measured after 48 hours and found to be within normal limits. The results were subjected to Student's t-test after equivalent variances and normal distribution of the data had been checked. Differences at $p < 0.05$ were considered significant.

Results

The anaesthetic technique proved to be entirely successful for these patients. No problems were encountered with unacceptable variations in pulse rate or blood pressure. One of the features was rapid recovery from anaesthesia but neither group was clinically faster than the other. Patients were sitting up, breathing oxygen, before they left theatre, and were sitting out of bed after 4 hours in the high dependency area. Opiate analgesics were not withheld if required but the laparotomy wound was not associated with severe pain. Most of the patients were able to walk the following morning.

The results in Fig. 1 show a marked difference in serum fluoride concentration between the two groups that is statistically significant. Serum fluoride in enflurane patients increases faster, to a higher peak (31.5 μmol/litre, maximum result) and is maintained longer than in isoflurane patients (7.9 μmol/litre). Renal function was not specifically investigated postoperatively but no patient developed abnormal blood urea or electrolytes. The serum fluoride levels encountered, although higher than normal, did not approach those associated with renal failure.

Discussion

Morbid, gross or severe obesity has been defined as 45.5 kg overweight, or twice the normal ideal

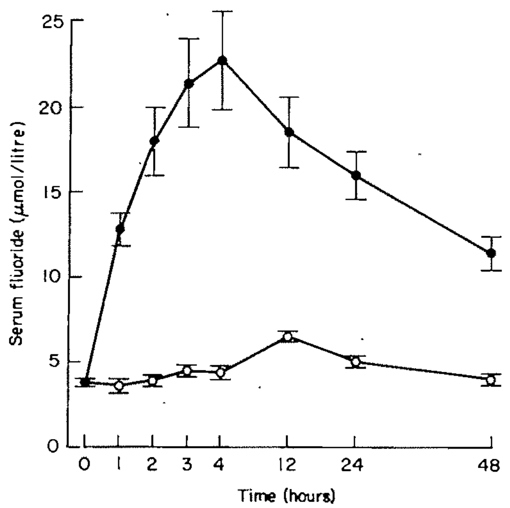

Fig. 1. Serum inorganic fluoride levels after enflurane anaesthesia (●) and isoflurane anaesthesia (○) (mean, SE).

weight for height in the Metropolitan Life Insurance tables. The ideal weight in kilograms can be calculated by subtracting 100 from the height in centimetres (Broca Index). Doubling the ideal weight determines morbid obesity for that person. The most useful index for measuring overweight has proved to be weight/height^2 (in kg/sq. m), the body mass index or BMI. It produces a single number and is least affected by height. Acceptable values for BMI are 20–25. Obesity is taken to start at a BMI of 30, and morbid obesity at 40. Men of this weight have at least 200% the mortality of people with normal acceptable weight.[11] There are no significant differences between men and women. Serum fluoride concentrations in the obese increase to a higher peak level after enflurane anaesthesia than after isoflurane anaesthesia. The peak occurs 2–4 hours after the end of the anaesthetic and lasts for about 12 hours. This increase is greater than that found in patients of normal weight.[4] Serum fluoride level in the isoflurane group did not increase significantly above that found in patients of normal weight.

It has been known for many years that inhalational agents are not exhaled totally unchanged by the lungs but are broken down by microsomal enzyme systems in the liver, kidney and brain. Metabolism does not appear to be an important factor in the recovery of consciousness following anaesthesia but it does indicate biochemical reactivity, and has implications for toxicology. In humans, isoflurane metabolism is one-tenth to one-hundredth that of other presently available halogenated anaesthetics.[8] This is related in part to its physical stability and resistance to alteration and partly to the more rapid elimination during recovery. Some inorganic fluoride is found after isoflurane administration but the amounts are very small, of the order of 5 μmol/litre.[9,10]

Metabolism may be increased or altered by a number of variables. Important considerations include patient factors such as genetic variation, race, exercise, fasting, low hepatic blood flow, hypoxia and drugs; enzyme factors such as inducing agents, alcohol, age, sex, diet and smoking habits; and substrate factors, for example, solubility and dose of the inhalational agent. The substrate factors seem the most important determinants of retention and subsequent biotransformation of the drug. The higher the oil–gas solubility coefficient and the longer the duration, the greater will be the amount of anaesthetic present for metabolism. In addition, chronic exposure leads to more complete transformation. With as many relevant factors as this, it is not surprising that a great degree of variability has been found in studies of anaesthetic metabolism.

The main pathway of isoflurane metabolism is thought to begin by insertion of an active oxygen atom into the ethyl α C–H bond. The unstable compound that results, is hydrolysed to difluoromethanol and trifluoroacetic acid. The first is hydrolysed to formic acid with the release of two fluoride ions, the second has been found to be the major source of organic fluoride.[12,13] Reductive metabolism does not appear to occur and free radicals from isoflurane metabolism under reductive conditions have not been found.[14] Liver enzyme induction with drugs such as isoniazid may be expected to increase metabolism of the halogenated anaesthetic agents, but *in vivo* studies have shown that this increase does not occur with isoflurane, unlike enflurane.[15]

The reasons why obese patients should metabolise to a greater extent are not fully understood, but there is no doubt that it does occur. Young *et al.*[3] found a high mean peak serum fluoride of 56 + 6 μmol/litre in 31 obese patients under methoxyflurane anaesthesia for 3 hours, and four patients had peak values of 90 μmol/litre

or more. In the repeat halothane/enflurane study of Dundee *et al.*,[16] one of the most significant findings was the increased abnormality of liver-damage enzymes which occurred in 48% of obese patients under halothane, against 10% of normals. Obesity has been associated with an increased incidence of halothane hepatitis.[17] Bentley *et al.*[4] found enflurane metabolism in morbidly obese patients to be 65% greater than in controls of normal weight, and serum fluorides increased from 17 to 28 μmol/litre. Metabolism was found to occur mostly in the period after surgery, reaching a peak 4–12 hours post-operatively. The rate of absorption into bone influences the size of the peak, and corrections can be made to allow for bone mass. Two morbidly obese patients had peak fluoride levels of 50 and 70 μmol/litre after enflurane.[2,18] The mechanism is unknown. It is possible that there may be increased uptake of lipid-soluble anaesthetic by a large amount of adipose tissue which forms a reservoir and allows more prolonged release and more complete biodegradation.

Certainly, many obese patients have fatty infiltration of their liver, which may act as a sump and cause higher liver concentrations of these drugs. The liver blood supply to a large, heavy organ may easily be reduced, which leads to relative hypoxia and switching to a more reductive metabolic pathway. These are all hypotheses, for which there is yet little evidence.

Which anaesthetic agent would provide the least risk of organ toxicity? Prudence dictates the cautious use of halothane or enflurane in anaesthesia for morbidly obese patients. In this study, peak serum fluoride levels averaged 22.7 μmol/litre in obese patients 2 hours after the end of enflurane anaesthesia. This is similar to values reported previously.[4] In contrast, the peak fluoride after 2 hours of isoflurane anaesthesia was 6.5 μmol/litre, which is not significantly different from that reported for normal weight controls.[10] Isoflurane and enflurane are both equally suitable clinically for anaesthetising morbidly obese patients but, when organ toxicity is taken into consideration, we suggest that isoflurane may be the anaesthetic agent of choice.

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The influence of anaesthesia on the acute phase protein response to surgery

P. J. SIMPSON, S. G. RADFORD AND J. A. LOCKYER

Summary

The influence of anaesthesia on the peri-operative changes in acute phase protein concentrations was studied in 18 patients undergoing elective cholecystectomy. A standard anaesthetic technique was supplemented either by one of two different doses of fentanyl, or by halothane. Eleven proteins were studied but the acute phase response was significantly altered by the anaesthetic technique for only two, fibrinogen and antichymotrypsin. The concentration of these proteins tended to be lower with 2–3 μg/kg fentanyl than with either halothane or fentanyl 12 μg/kg. There was no evidence of variation in stress suppression between the three techniques. The mechanism of any anaesthetic influence on the acute phase response is uncertain and this study is too small to assess its clinical significance.

Key words

Analgesics, narcotic; fentanyl.
Anaesthetics, inhalational; halothane.
Protein; acute changes.

The acute phase response to injury is an integral part of the inflammatory process. Crockson *et al.*[1] have described the changes which occur in acute phase protein concentrations during and after surgery. Peak concentrations of different acute phase proteins occur at varying intervals after surgery.[1–3] Maximum concentrations of C-reactive protein and α-1-antitrypsin tend to occur within 48 hours, while orosomucoid and fibrinogen levels do not peak until 3–4 days postoperatively.[1]

C-reactive protein responds in most types of inflammatory response[4] but changes in the concentrations of certain other proteins have been particularly associated with distinct conditions. For example, C3 complement activation is seen in Gram-negative septicaemia,[5] fibrinogen and fibronectin concentrations are changed in disorders of coagulation and fibrinolysis,[6] α-1-antitrypsin levels are markedly increased in active hepatitis and cirrhosis of the liver[7] and orosomucoid is raised dramatically in pancreatitis, peritonitis and gastrointestinal infections.[8] No association, however, has yet been demonstrated between the postoperative elevations in acute phase proteins and the anaesthetic administered to the patient.

Variations in anaesthetic technique are known to alter the stress response to surgery[9] and it is possible that such differences may be accompanied by variations in the acute phase response. This study was designed to investigate the in-

P.J. Simpson, MD, FFARCS, Consultant, Senior Lecturer, S.G. Radford, FIMLS, Senior Technician, J.A. Lockyer, Technician, Sir Humphry Davy Department of Anaesthesia, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

fluences of three different forms of anaesthetic supplementation upon the postoperative changes in acute phase protein concentrations following elective surgery.

Methods

Three groups were studied; each consisted of six patients undergoing elective cholecystectomy. The patients were randomly distributed between the three anaesthetic groups; four were male and 14 were female. Patients were not studied if they were suffering from any diseases or receiving drugs known to influence acute phase protein concentrations, or had an acute infection, impaired hepatic function or jaundice. The study was approved by the hospital ethical committee and all patients gave their informed consent to the study and to the daily sampling of venous blood during the postoperative period.

One hour after premedication with papaveretum 0.25 mg/kg and hyoscine 0.006 mg/kg, anaesthesia was induced with thiopentone 5 mg/kg. Alcuronium 0.3 mg/kg was given prior to tracheal intubation and anaesthesia maintained using intermittent positive pressure ventilation of the lungs with 67% nitrous oxide in oxygen via a Manley ventilator. The tidal volume was 10 ml/kg with a fresh gas flow rate of 120 ml/kg/minute. Anaesthesia was supplemented with one of the following anaesthetic techniques: group 1 (1 male), fentanyl 12 μg/kg; group 2 (3 males), fentanyl 2–3 μg/kg; group 3 (0 males), halothane 0.5–0.75%.

At the end of operation, neuromuscular blockade was reversed with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg, and the patients returned to the recovery room for 2–3 hours prior to return to the ward. All operations were performed in the early afternoon to minimise diurnal variation, and by one of two consultant surgeons to minimise differences in surgical technique.

Peroperative intravenous fluid replacement was administered at the rate of 7.5 ml/kg/hour for the first hour and 5 ml/kg/hour thereafter, using compound sodium lactate (Hartmann's) solution. Blood loss was also replaced with Hartmann's solution and none of the patients included in the study required peri-operative blood transfusion. Postoperative intravenous fluid therapy was given at the rate of 2 ml/kg/hour using physiological saline and 5% dextrose. Papaveretum 0.25 mg/kg was given for postoperative analgesia, together with metoclopramide 0.15 mg/kg when required for the control of nausea.

At each sampling interval, a total of 14 ml of venous blood was collected for acute phase protein, glucose and cortisol estimations. The samples were immediately centrifuged, separated and stored at $-20°C$ prior to assay. Blood was collected from the antecubital fossa of the non-infusion arm at the intervals shown in Table 1;

Table 1. Sampling intervals.

Sample	Time
1	Pre-operative
2	Postoperative
3	Postoperative + 3 hours
4	Day 2
5	Day 3
6	Day 4
7	Day 5
8	Day 6
9	Day 8

the later daily samples were collected between 09:00 and 11:00 hours. Acute phase protein concentrations were assayed by rocket immunoelectrophoresis using commercially available antisera. Table 2 shows the proteins assayed

Table 2. Acute phase proteins studied.

Protein	Normal range (g/litre)
Orosomucoid	0.5–1.2
C3	0.55–1.2
C4	0.2–0.6
Fibrinogen	2.0–4.5
Plasminogen	0.1–0.3
Caeruloplasmin	0.15–0.6
α-1-Antitrypsin	2.0–4.0
α-2-Macroglobulin	1.5–4.0
C-reactive protein	0–0.008
C1 esterase inhibitor	0.2–0.4
Antichymotrypsin	0.3–0.6

together with their normal reference values. The coefficient of variation for protein measurements was 5% and for cortisol estimation 9% against laboratory controls. The accuracy of cortisol estimation, related to the 'All Laboratories Trimmed Mean', was 0.24%. Blood sugar and serum cortisol were measured in the department of clinical biochemistry, by autoanalysis and radio-immunoassay, respectively.

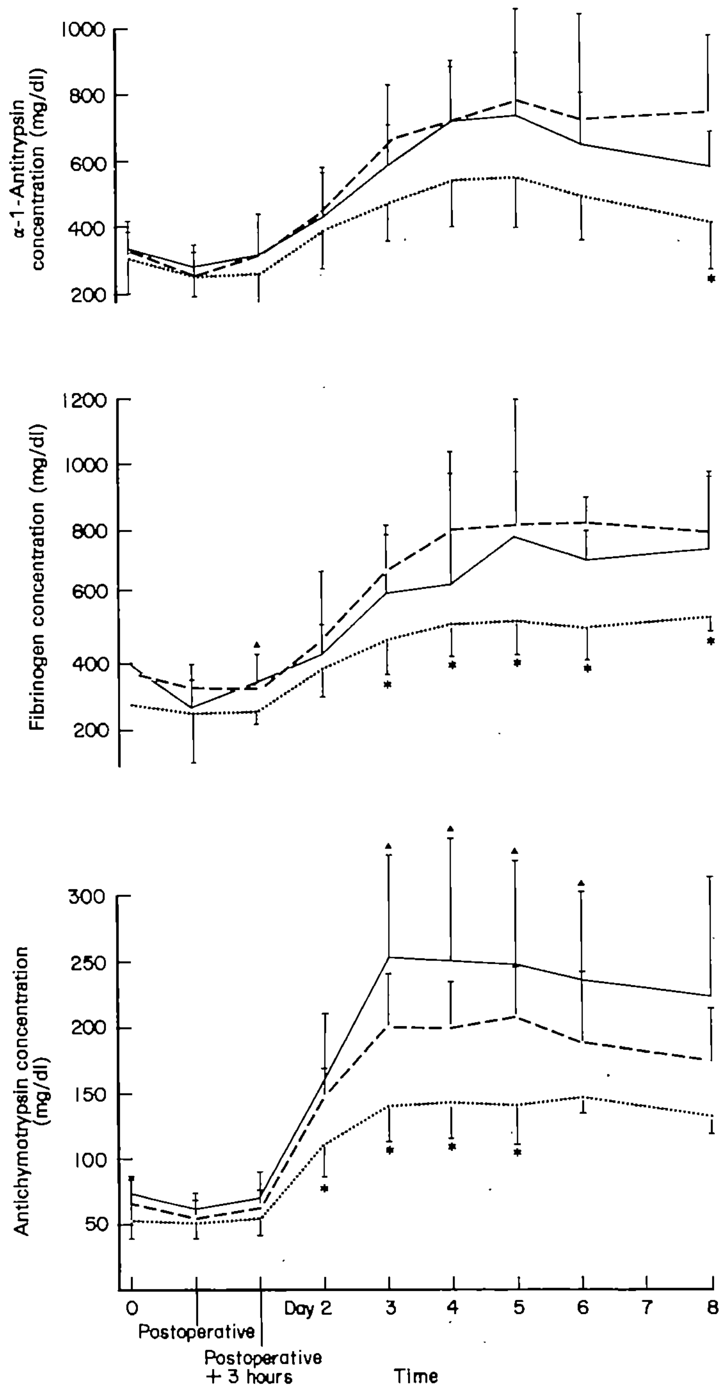

Fig. 1. Mean concentrations, together with standard deviations, of α-1-antitrypsin, fibrinogen and antichymotrypsin for the three anaesthetic groups studied. Significant differences between low dose fentanyl and halothane are indicated by asterisks and those between high and low dose fentanyl, by triangles. ——, Fentanyl 12 μg/kg, ······, fentanyl 2–3 μg/kg; – –, halothane.

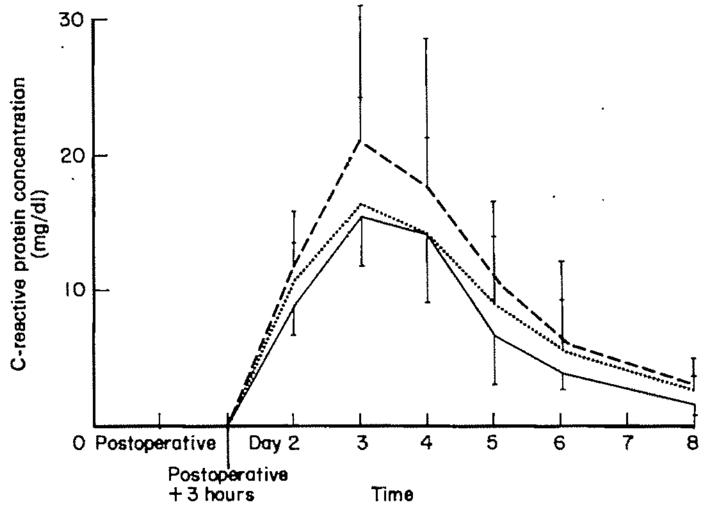

Fig. 2. Mean concentrations, together with standard deviations, of C-reactive protein for the three anaesthetic groups studied. ——, Fentanyl 12 μg/kg; ······, fentanyl 2–3 μg/kg; ---, halothane.

Haematocrits were routinely measured on each sample.

Statistical methods. Overall differences in acute phase protein response were tested using two-way analysis of variance. The unpaired Student's *t*-test was then used to identify differences between the individual proteins that occurred at particular times.

Results

Serial concentrations of 11 acute phase proteins were measured (Table 2) but only two, fibrinogen and antichymotrypsin, showed prolonged significant differences in response between the three anaesthetic techniques. For these two proteins, the mean values together with standard deviations are shown in Fig. 1 for each of the anaesthetic techniques used. Times at which significant differences between the lower dose of fentanyl and halothane were demonstrated, are shown by asterisks; differences between the two doses of fentanyl are shown by triangles. Lower dose fentanyl supplementation tended to produce lower protein concentrations than either of the other two techniques.

A similar pattern was observed with α-1-antitrypsin but the only significant difference occurred between halothane and low dose fentanyl on the 8th postoperative day (Fig. 1). C-reactive protein concentrations were similar in all three anaesthetic groups (Fig. 2). Since, for most of the proteins studied, no significant differences were observed between the three groups, the results have been pooled and the overall means and standard deviations are shown in Table 3, to provide a set of reference data for cholecystectomy.

The blood sugar and cortisol response followed a similar pattern in all three groups (Fig. 3), apart from the three points indicated, where statistically significant differences were observed. Since oral glucose intake was not controlled, however, these differences were considered unimportant.

The haematocrits measured were all between 0.33 and 0.50, despite the avoidance of transfusion in all patients. The daily variation between samples from individual patients, however, was minimal and certainly insufficient to affect the other haematological and biochemical measurements made.

All patients had a clinically uneventful postoperative course and none developed significant pulmonary or abdominal complications which could be linked with changes in acute phase protein concentration.

Discussion

Of the 11 proteins studied, only fibrinogen and antichymotrypsin showed any significant dif-

Table 3. Peri-operative acute phase protein concentrations, g/litre.

Sample	Protein										
	Fibrinogen	Antichymo-trypsin	α-1-Antitrypsin	C-reactive protein	C3	C4	Oroso-mucoid	α-2-Macro-globulin	Caerulo-plasmin	C1 esterase inhibitor	Plasminogen
1											
n	17	18	18		17	18	18	18	18	18	16
Mean (SD)	3.52 (1.14)	0.65 (0.17)	3.19 (0.79)	N/D	0.99 (0.39)	0.45 (0.11)	0.83 (0.22)	2.39 (0.57)	0.45 (0.13)	0.36 (0.10)	0.14 (0.02)
2											
n	17	18	18		17	18	18	17	18	17	16
Mean (SD)	2.86 (1.09)	0.58 (0.13)	2.66 (0.68)	N/D	0.92 (0.34)	0.41 (0.11)	0.78 (0.33)	2.27 (0.66)	0.41 (0.12)	0.32 (0.09)	0.14 (0.03)
3											
n	16	18	18		17	18	18	17	18	18	15
Mean (SD)	3.11 (0.86)	0.64 (0.17)	3.00 (1.05)	N/D	0.92 (0.39)	0.42 (0.13)	0.78 (0.30)	2.25 (0.65)	0.42 (0.13)	0.33 (0.08)	0.14 (0.02)
4											
n	18	18	18	18	18	18	18	18	18	18	16
Mean (SD)	4.31 (1.33)	1.40 (0.39)	4.24 (1.22)	0.11 (0.03)	1.01 (0.41)	0.44 (0.13)	1.20 (0.35)	2.38 (0.66)	0.45 (0.13)	0.34 (0.10)	0.14 (0.03)
5											
n	17	17	17	17	17	17	17	17	17	17	15
Mean (SD)	5.85 (1.65)	2.00 (0.69)	5.66 (1.51)	0.17 (0.07)	1.10 (0.48)	0.48 (0.13)	1.56 (0.52)	2.18 (0.64)	0.45 (0.12)	0.39 (0.10)	0.13 (0.02)
6											
n	17	17	17	18	18	18	18	18	18	18	16
Mean (SD)	6.64 (2.73)	1.97 (0.69)	6.62 (1.76)	0.15 (0.08)	1.22 (0.50)	0.52 (0.15)	1.85 (0.79)	2.33 (0.72)	0.48 (0.13)	0.45 (0.11)	0.15 (0.05)
7											
n	18	18	18	18	18	18	18	18	18	18	16
Mean (SD)	7.18 (2.82)	2.00 (0.69)	6.91 (2.23)	0.09 (0.05)	1.24 (0.46)	0.57 (0.17)	1.77 (0.67)	2.21 (0.66)	0.52 (0.14)	0.49 (0.14)	0.16 (0.04)
8											
n	15	16	16	16	16	16	16	16	16	16	14
Mean (SD)	6.71 (1.77)	1.96 (0.61)	6.42 (2.32)	0.05 (0.04)	1.32 (0.54)	0.58 (0.14)	1.81 (0.54)	2.34 (0.85)	0.51 (0.17)	0.53 (0.13)	0.16 (0.04)
9											
n	14	14	14	14	14	14	14	14	14	14	12
Mean (SD)	6.41 (2.48)	1.79 (0.67)	5.95 (2.03)	0.02 (0.01)	1.39 (0.49)	0.61 (0.11)	1.86 (0.63)	2.43 (0.78)	0.49 (0.15)	0.50 (0.15)	0.18 (0.07)

N/D, not done.

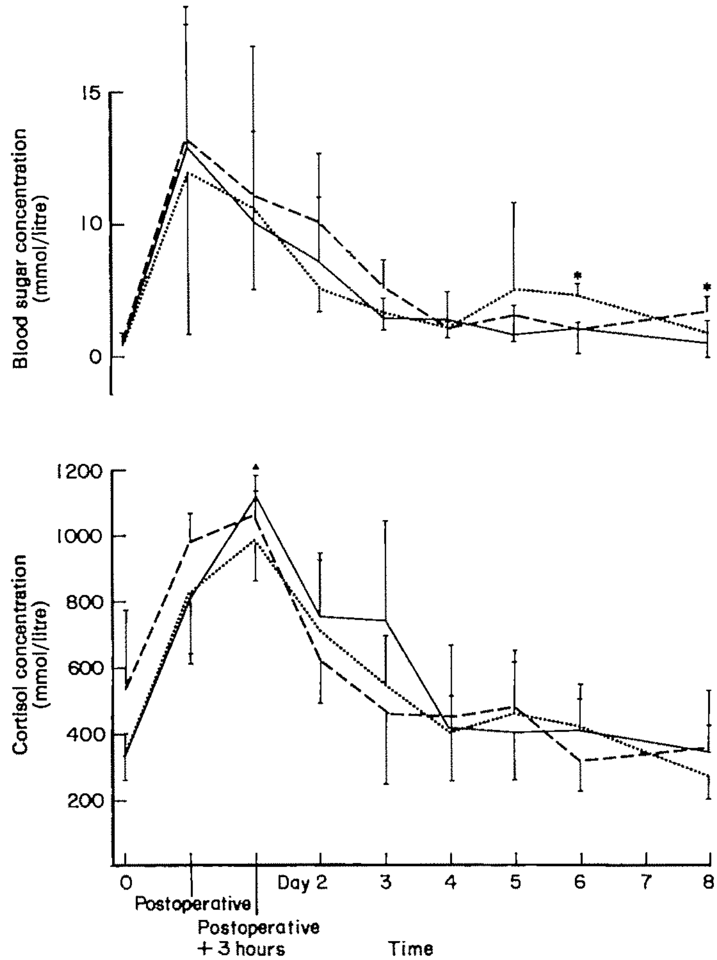

Fig. 3. Mean concentrations, together with standard deviations, of blood sugar and cortisol for the three anaesthetic groups studied. Significant differences between low dose fentanyl and halothane are indicated by asterisks and those between high and low dose fentanyl, by triangles. ——, Fentanyl 12 μg/kg; ······, fentanyl 2–3 μg/kg; – – –, halothane.

ference in acute phase response which could be related to differences between the three chosen anaesthetic techniques. The lower (2–3 μg/kg) dose of fentanyl produced a significantly smaller acute phase response than either halothane or the higher (12 μg/kg) dose of fentanyl. A similar trend was observed for α-1-antitrypsin (Fig. 1) but this was not statistically significant in this small sample.

Exogenous steroids generally suppress the acute phase response in chronic inflammatory conditions. If the same were true of endogenous steroids, less effective stress suppression might be expected to produce a more pronounced acute phase response. The higher dose fentanyl supplementation used was modest in relation to doses which are used for deliberate stress suppression[9] but it was the highest dose which was judged compatible with normal recovery of spontaneous ventilation at the end of operation without the need to give naloxone. It was anticipated, nonetheless, that the higher dose of fentanyl would suppress stress more effectively than the lower dose.

In general, the biochemical results do not support this, although Fig. 3 suggests significantly higher cortisol concentrations 3 hours postoperatively in the higher dose fentanyl

group compared with the low. This observation is intriguing and, if it can be substantiated, would be surprising for two reasons; firstly, because fentanyl in lower doses should suppress peak cortisol concentrations more than higher doses, and secondly, because having done so it should produce a less pronounced acute phase response. These apparent anomalies may possibly reflect differences in the development of the acute phase response between acute and chronic conditions.

Irrespective of how anaesthesia might alter the acute phase protein response, there is no indication that any clinical significance can be attached to any such alteration. One can speculate that a technique which suppresses stress and the acute phase response may not be beneficial, since the maintenance of an intact inflammatory reaction to injury appears to be so important to normal recovery. These questions can be answered only by study of anaesthetic techniques which have a greater effect on a wider range of acute phase proteins, and by the inclusion of sufficient numbers of patients to allow an estimate of relative morbidity.

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Nalbuphine for obstetric analgesia

A comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA)

M. FRANK, E. J. McATEER, R. CATTERMOLE, B. LOUGHNAN, L. B. STAFFORD AND A. M. HITCHCOCK

Summary

A double-blind, randomised study of 60 patients who received intravenous increments of nalbuphine 3 mg or pethidine 15 mg by patient-controlled analgesia during the first stage of labour, was carried out. Pain intensity, sedation, uterine contractions, maternal cardioventilatory variables and fetal heart rate were recorded as well as any side effects. Apgar scores, time to sustained respiration and resuscitative measures required for the neonate were noted at delivery. Modified neonatal neurobehavioural studies and a retrospective assessment of maternal analgesia, satisfaction and tolerance were also carried out. Group mean values of pain scores of nalbuphine-medicated primiparous women were statistically significantly lower than those of pethidine-medicated patients ($p < 0.01$). Other assessments did not demonstrate a statistical significance between the two groups.

Key words

Analgesics, narcotic; pethidine, nalbuphine.
Analgesia; obstetric.

A parenteral formulation of nalbuphine, a synthetic agonist–antagonist analgesic of the phenanthrene series, has been used for the relief of postoperative pain and as an analgesic supplement to surgical anaesthesia.[1,2] It has been shown to have a potency of 60–80% when substituted for morphine[3,4] but a ceiling effect for ventilatory depression has been demonstrated with nalbuphine.[5] Nausea and vomiting have been found to occur less often than with pethidine[6] and it has been shown to have fewer psychomimetic reactions than pentazocine.

This study was undertaken to compare the analgesic efficacy, complications and the effects on labour, the fetus and neonate of nalbuphine compared with pethidine; both drugs were administered intravenously on demand via a Cardiff Palliator.[7]

Method

A double-blind study was carried out on 60 mothers of ASA grade 1 who required pain relief in labour. Those not studied were mothers whose pregnancy was less than 38 weeks or longer than 42 weeks, patients who elected to have epidural analgesia or who had already received opioid analgesics, those who received

M. Frank, MB, ChB, FFARCS, E.J. McAteer, MB, ChB, FFARCS, Senior Lecturers, R. Cattermole, MB, ChB, FFARCS, B. Loughnan, BSc, MB, ChB, FFARCS, Lecturers, L.B. Stafford, SRN, A.M. Hitchcock, SRN, Research Nurses, Anaesthetic Unit, London Hospital, Whitechapel, London E1 1BB.

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monoamine oxidase inhibitors or tricyclic antidepressants within 2 weeks of the study, or when the fetus was at risk.

The study was approved by the local ethical committee and informed consent was obtained from each patient at an antenatal visit in their last 4 weeks of pregnancy or on admission to the delivery suite before labour became established. The 60 patients were randomly allocated into two groups. Patients in group 1 received nalbuphine and those in group 2, pethidine.

The analgesic medication commenced when the patient expressed a need for pain relief in the first stage of labour. Pethidine 200 mg or nalbuphine 40 mg was diluted with 0.9% saline to a volume of 20 ml in a syringe which was then placed in the Cardiff Palliator. The palliator was set to give a volume of 1.5 ml over 3 minutes when a demand was made by pressing the demand button twice within the period of 1 second, and the lockout time was 10 minutes. With these settings, patients in group 1 received 3-mg increments of nalbuphine with a maximum of 18 mg in any 60-minute period, and patients in group 2 received 15-mg increments of pethidine with a maximum of 90 mg in 60 minutes. The total maximum dose of nalbuphine was 42 mg and of pethidine, 210 mg. Medication was stopped at the commencement of the second stage of labour, or if side effects occurred or the patient expressed a desire for an alternative method of pain relief.

Bearing in mind the accelerating increase of pain intensity in labour, the times of onset of the first and second stages of labour and of the first and last doses of the analgesic, were recorded in addition to the total numbers of doses the patients received and their intervals, in order to assess the epoch within labour during which the test medication was administered.

Assessments

The following assessments were made prior to the first dose of pethidine or nalbuphine and then half-hourly for the duration of the medication.

Mother. Pain was assessed on a five-point scale; the mother was questioned towards the end of a contraction and asked to describe her pain in one of the terms shown in Table 1. The number of mothers who requested Entonox in addition to the test medication, was noted in the two groups; in these mothers Entonox was withheld during their half-hourly pain assessment. Sedation was assessed during and between uterine contractions, on a three-point scale (Table 1). Arterial blood pressure and heart rate were monitored using an Accutor automatic monitor with printer. Ventilatory rate was recorded by the observer. Any side effects complained of by the mother, or noted by the observer, were recorded. Progress of labour was monitored and frequency and strength of contractions were noted (the contraction was assessed by the observer), as shown in Table 1.

Table 1. Half-hourly maternal assessments and their grading during medication.

	Score	Assessment
Pain	1	None
	2	Mild
	3	Moderate
	4	Severe
	5	Very severe
Sedation	1	Awake
	2	Drowsy
	3	Asleep
Uterine contractions	1	Good
	2	Moderate
	3	Poor

Infant. Fetal heart rate during medication was recorded. Those infants who were delivered within 4 hours of the last dose of the test drug were assessed at delivery and at 6–10 hours. The Apgar score and time to sustained respiration (TSR) were recorded at delivery and any resuscitative measures required were noted. Neurobehavioural assessments at 6–10 hours after delivery were based on a modified new neurological and adaptive capacity scoring system (NACS).[8] Consolability, visual and aural stimuli, and the infant's habituation to these stimuli have been found to be the most sensitive indicators of neurobehavioural changes in the neonate following maternal administration of pethidine; the best score is 10 and the worst, 0.

Postpartum follow-up. The patients were interviewed and questioned 24 hours after delivery to evaluate their retrospective assessment of the treatment. Analgesic efficacy and tolerance to the medication were scored as poor, acceptable or excellent, and their overall satisfaction, and whether they would have the procedure again, was noted as yes, no or unsure. The observer

Table 2. Demographic data of the patients studied: values expressed as mean (SD).

	Nalbuphine (n = 30)	Pethidine (n = 30)
Mean age, years	23.5 (4.19)	25.1 (4.91)
Mean weight, kg	77.0 (13.8)	72.5 (11.6)
Mean height, cm	160.6 (5.79)	157.7 (6.44)
Mean length of pregnancy, weeks	39.9 (1.12)	39.9 (1.21)
Primiparous mothers	24	18
Multiparous mothers	6	12

Table 3. Mean intervals in minutes (SD) to illustrate epoch of analgesic medication within first stage in group 1 (nalbuphine) and group 2 (pethidine).

Interval	Nalbuphine	Pethidine
Onset of first stage to first dose	356.0 (393)	316.0 (288)
First to last dose for patients who received maximum dose	296.7 (95.6)	266.1 (113.4)
First dose to delivery for patients who received maximum dose	544.9 (250.1)	504.7 (230.1)
First dose to delivery for patients who received less than maximum dose	249.6 (295.0)	209.4 (191.3)

also scored analgesic efficacy and tolerance on the same scale as the patient.

Analysis of the results was performed using generalised linear models and nonparametric methods as appropriate.

Results

Demography. Distributions of age, weight and height in the two groups are shown in Table 2. The distribution of length of pregnancy was similar for both groups with a mean of 39.9 weeks in each group. The number of patients who had artificially ruptured membranes was 18 in group 1 and 19 in group 2. There was a preponderance of primiparous patients in the group of mothers who received nalbuphine (Table 2) and this was taken into account during analysis.

Epoch of labour. The mean cervical dilatation at first dose was 3.47 cm (SD 1.71) and 3.60 cm (SD 1.49) in groups 1 and 2, respectively. The time from onset of contractions to first dose was not significantly different in the two groups: 356 minutes (SD 393) and 316 minutes (SD 288), respectively. The time from first dose to delivery was analysed separately for those patients who received the maximum dose of nalbuphine or pethidine. First dose to delivery interval was similar in both groups (Table 3). Last dose to delivery intervals were similar in those patients who had received less than a maximum dose; in those who had the maximum dose the median time was longer in group 1 (292 minutes, SD 216.7) than in group 2 (127 minutes, SD 199.0), but the difference was not statistically significant.

The time from first dose to last dose for those who had the maximum dose was similar, 296.7 minutes (SD 95.6) and 266.1 minutes (SD 113.4) in groups 1 and 2, respectively.

Pain. Mean pain scores in the two groups, before medication and half-hourly thereafter, are shown in Fig. 1. The predose mean pain scores in the randomly allocated groups were significantly different ($p < 0.01$). There was a statistically significant difference in the opposite direction ($p < 0.05$) in the mean values between the groups during the first 2 hours after commencement of medication. Changes in mean pain scores from predose values over the periods of 0.5–1 hour, 0.5–2.5 hours and 0.5–9 hours in the two groups were also analysed; a significant difference ($p < 0.01$) was found between the two medications (Table 4). When the two groups were divided according to parity, the differences between the changes from predose values were more marked in the primiparous group and were

Table 4. Comparison of changes in mean pain scores from predose values between the two groups.

	Assessment time		
	0.5–1 hour	0.5–2.5 hours	0.5–9 hours
Nalbuphine	−0.79	−0.73	−0.58
Pethidine	0.20	0.23	0.29
p	<0.01	<0.01	<0.01
SED	0.30	0.29	0.27

p, Level of significance between the two medications; SED, standard error of the difference.

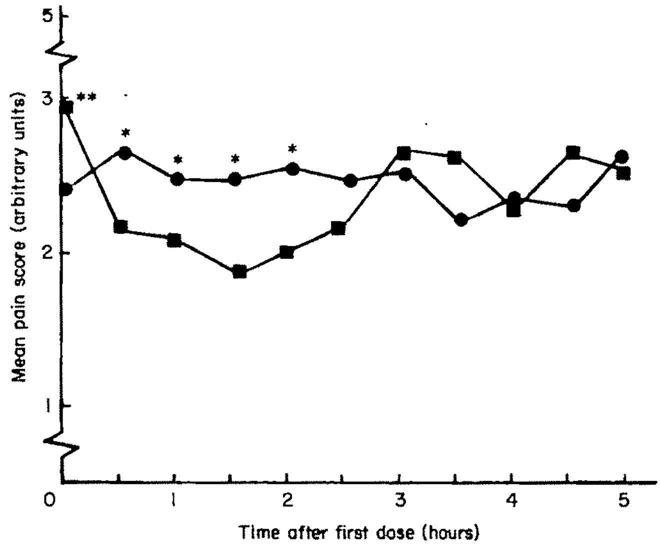

Fig. 1. Mean pain scores before and during medication for patients who received pethidine (●) or nalbuphine (■). ** $p < 0.01$, * $p < 0.05$, levels of significance for comparison between the two groups. The difference in the predose values is in the opposite direction from that found in the postmedication scores.

Table 5. Comparison of changes in mean pain scores from predose values between the two groups according to parity.

	Assessment time		
	0.5–1 hour	0.5–2.5 hours	0.5–9 hours
Primiparae			
Nalbuphine	−0.96	−0.94	−0.68
Pethidine	0.25	0.22	0.35
p	<0.01	<0.01	<0.01
SED	0.36	0.35	0.32
Multiparae			
Nalbuphine	−0.33	−0.27	−0.27
Pethidine	0.08	0.18	0.18
p	NS	NS	NS
SED	0.57	0.56	0.52

p, Level of significance between the two medications; SED, standard error of the difference.

not significant in the multiparous patients (Table 5).

Demand rate and dose distribution were similar for both groups. The median demand rate for the multiparous mothers in both groups was 0.13 ml/minute. The rates for the primiparous mothers were 0.07 and 0.09 ml/minute for nalbuphine and pethidine, respectively. Eleven patients in group 1 and 9 in group 2 received the maximum dose.

The percentage of patients who used Entonox before medication was higher in group 1 (60%) than in group 2 (33%). The percentages became comparable during dosing (38 and 46%, respectively). The number of patients who received a Syntocinon infusion was higher in group 2 in both the multiparous and primiparous mothers, but this was not statistically significant.

Sedation. There was no significant difference between the groups in level of sedation either during or between uterine contractions.

Cardioventilatory changes. There was no significant difference between the groups either in arterial blood pressure or heart rate before or during medication. Ventilatory rate was also similar throughout the study; both groups had medians of 20 breaths/minute.

Progress of labour. The intervals between contractions were similar for both groups before and during medication. The strength of contraction was also similar for both groups. The distribution of length of second stage, taking into account parity, was similar in both groups. The times in group 1 were 56.2 minutes (SD 52.2) for primiparous and 24.0 minutes (SD 20.5) for multiparous mothers and in group 2, 61.3 minutes (SD 25.4) and 14.6 minutes (SD 4.25), respectively.

Side effects. One patient in group 2 withdrew due to inadequate analgesia, none in group 1. No patient was withdrawn from the study because of intolerable adverse effects of the medication.

The most common side effect was vomiting; seven mothers who received nalbuphine and 10 who received pethidine were affected. The proportion of patients with any side effects was higher in the pethidine-medicated patients (13) than in those who received nalbuphine (9), but this was not statistically significant.

Twenty-four hour follow-up. At the postpartum assessment, 72% of mothers who received nalbuphine regarded it as good or excellent for pain relief compared to 55% of those who had received pethidine. When the groups are subdivided into primiparous and multiparous mothers, the response to the medication was similar in the primiparous mothers: i.e. 74% and 72% in groups 1 and 2, respectively, regarded the medication as good or excellent. When the multiparous mothers were questioned, four out of six in group 1 and three out of 11 in group 2 regarded the medication as good or excellent.

Tolerance was similar in both groups, as was overall satisfaction. Seventeen out of 19 primiparous and five out of six multiparous patients who received nalbuphine said they would have the same form of pain relief again. Of the mothers who received pethidine, 15 out of 18 and six out of 11, respectively, would have the same analgesia in a subsequent labour. These differences did not reach statistical significance.

Infants. The mean fetal heart rates before and during medication were similar in the two groups. Those infants born within 4 hours of the last dose of medication had Apgar scores of 9 or 10 at 5 minutes in both groups, their time to sustained respiration was less than 60 seconds and they did not require active resuscitation, except for one infant in group 2 who was moderately depressed (Table 6).

Table 6. Fetal and neonatal assessments: values expressed as mean (SD).

	Nalbuphine	Pethidine
Fetus	(n = 30)	(n = 30)
Heart rate		
Premedication	133.0 (11.18)	133.3 (13.36)
During medication	127.4 (11.16)	126.8 (11.46)
Neonates (those delivered within 4 hours of last medication)	(n = 18)	(n = 23)
Apgar score at 5 minutes		
>7	18	22
4–6	0	1
<3	0	0
TSR		
<30 seconds	16	20
>30 seconds	2	3
Resuscitation		
None or oxygen only	18	22
Intubation	0	1

TSR, time to sustained respiration.

There was no statistically significant difference between the two groups when the modified NACS was analysed (Table 7).

Discussion

Pethidine is the most widely accepted and practised method of obstetric analgesia in the UK. However, studies have shown a variable analgesic efficacy; 40[9] to 75%[10] of mothers who receive it, find the pain experienced following its administration still unacceptable or unsatisfactory. In addition, various side effects associated with pethidine are disadvantageous in the obstetric situation. These include the ventilatory depressant effect on mother and neonate, the drug's peripheral vasodilatory property[11] and

Table 7. Neurobehavioural assessments 6–10 hours after delivery.

	Sound		Light	
	Nalbuphine (n = 17)	Pethidine (n = 23)	Nalbuphine (n = 17)	Pethidine (n = 23)
Response				
Vigorous	4 (24%)	4 (17%)	14 (82%)	18 (78%)
Mild	13 (76%)	18 (78%)	3 (18%)	5 (22%)
Absent	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Habituation				
0–6 stimuli	9 (53%)	12 (52%)	14 (82%)	15 (65%)
7–12 stimuli	8 (47%)	10 (44%)	3 (18%)	8 (35%)
Absent	0 (0%)	1 (4%)	0 (0%)	0 (0%)

delayed gastric emptying in a situation where a high gastric volume is one of the factors that predispose to regurgitation and aspiration pneumonitis.

The search for an analgesic method closer to obstetric requirements continues and analgesic drugs with agonist–antagonist properties might be more suitable if their analgesic efficacy is not inferior to that of pethidine. Nalbuphine is an analgesic with agonist and antagonist properties which has been found to have a ceiling ventilatory depressant effect and which, in previous studies, has been found to have fewer side effects than pethidine. It appears to have a lesser effect on delaying of gastric emptying[12] and does not share the addictive propensities of the opioid analgesics; its administration is not regulated by the conditions required by the narcotic analgesics. It was therefore considered appropriate to explore its suitability in obstetrics and, for this purpose, to compare it with the standard obstetric analgesic, pethidine. There are various inherent difficulties in the comparative assessment of analgesic drugs in relation to their relative analgesic properties and side effects. Pain is a subjective sensation and its measurement is subject to variable factors; labour is a further, not inconsiderable, addition to these difficulties. Patient-controlled analgesia (PCA) was chosen in this study since in addition to regular measurements of the patient's experience of pain, her analgesic requirements may also be assessed by the number and frequency of demands when the two analgesics are compared, taking into account their pharmacological properties including relative half-lives and accumulation. Clinically PCA may offer a better form of analgesia that enables the mother to tailor her analgesic needs to the increasing intensity of pain experienced as labour progresses, in contrast to the intramuscular route which may provide maximal analgesia in the earlier, less painful, interval.

In this study nalbuphine administered by PCA at a dose of 3 mg per demand produced better pain relief than pethidine in primiparous patients in the first stage of labour. In the group of patients who received nalbuphine, the mean pain score following commencement of PCA decreased when compared with the mean premedication value, while in the pethidine group the mean pain score increased; the difference in the two groups was statistically significant (Fig. 1). The increase in mean pain score following pethidine administration may be related to the increasing intensity of pain experienced as labour progresses. The demand rates were similar in the two groups, as was the length of labour. Nalbuphine has a longer half-life and therefore greater accumulation of this drug would be expected to result when the dosing is at similar intervals. This effect may have contributed to the improved pain relief experienced by the mothers who received nalbuphine.

The multiparous group showed the same trend from baseline values following nalbuphine or pethidine administration as the primiparae, but there was no statistical significance; however, numbers in this group were small. Other factors, including sedation, progress of labour and cardioventilatory changes, were not significantly different between the groups. A greater number of women in this study experienced side effects after they received pethidine but this did not reach statistical significance.

The effects on the fetus and neonate of the two different analgesics did not show any significant difference, as measured by the intrapartum fetal heart rate during medication, the Apgar scores, TSR and resuscitative measures required immediately after birth, and the modified neurobehavioural assessments at 6–10 hours postpartum.

In conclusion, in this study nalbuphine administered by PCA at a dose of 3 mg produced better analgesia in primigravidae than 15 mg pethidine per demand, without any increase in maternal or infant side effects.

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Gastric emptying and small bowel transit times in volunteers after intravenous morphine and nalbuphine

H. YUKIOKA, M. ROSEN, K. T. EVANS, K. G. LEACH, M. W. J. HAYWARD AND G. S. SAGGU

Summary

Gastric emptying half-times and small intestinal transit times were measured in a double-blind crossover study of 17 volunteers who received an intravenous injection of nalbuphine (5 or 10 mg), morphine (5 mg) or placebo. Both times were monitored using a gamma camera after a radioactive test meal and gastric emptying half-time was calculated. Small intestinal transit time was measured by the appearance of radioactivity in the caecum and also of hydrogen in end tidal air. Gastric emptying was prolonged over placebo by nalbuphine 10 mg, which had more effect than nalbuphine 5 mg or morphine 5 mg; morphine 5 mg had less effect than nalbuphine 5 mg. Small intestinal transit time was prolonged over placebo by nalbuphine 10 mg more than by nalbuphine 5 mg or morphine 5 mg, which had approximately equal effects. In these respects, the potency ratio of nalbuphine appears roughly equivalent to morphine. Small intestinal transit times measured by end tidal hydrogen concentration and gamma camera showed close agreement.

Key words

Analgesics, narcotic; morphine, nalbuphine.
Gastrointestinal tract; stomach, intestine.

Opioid drugs depress gastrointestinal function but there is little information on quantitative differences between agonists such as morphine and newer synthetic agonist–antagonist drugs. It would be of clinical importance to be able to predict the type and duration of the effect of each drug administered for pain relief. Therefore, to establish methodology, gastric emptying half-times and small intestinal transit times were measured in volunteers after low intravenous doses of morphine and nalbuphine.

Method

The effects of intravenous nalbuphine or morphine on gastrointestinal function were evaluated in healthy volunteers in a double-blind crossover study. Each volunteer gave written, informed consent and the study was approved by the hospital ethical committee. Volunteers were studied twice and were assigned at random to one of four groups that received intravenously nalbuphine 10 mg or saline placebo (group 1),

H. Yukioka, MD, Department of Anaesthesiology, Osaka City Hospital, Japan, M. Rosen, FFARCS, Professor in Anaesthetics, K.T. Evans, FRCP, FRCR, Professor of Radiology, K.G. Leach, PhD, BSc, Principal Physicist, M.W.J. Hayward, FRCS, FRCR, Senior Lecturer, G.S. Saggu, MSc, BSc, Physicist, University Hospital of Wales, Heath Park, Cardiff.
Correspondence should be addressed to Professor M. Rosen please.

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morphine 5 mg or placebo (group 2), nalbuphine 10 mg or morphine 5 mg (group 3), or nalbuphine 5 mg or morphine 5 mg (group 4). Drugs were administered in random order with an interval of 1–3 weeks between the two investigations. Since there is uncertainty about the potency ratio of nalbuphine to morphine, two dose levels of nalbuphine were tested.[1]

Volunteers fasted for 12 hours before the study. A standard test meal was eaten (approximately 90 g of scrambled eggs without additional fat and 120 g of baked beans) with 50 ml of water within 10 minutes. At the end of the meal the drug or placebo was injected in 1 ml over one minute between 09:00 and 10:00 hours. The injection was made into a cannula in an antecubital vein and flushed with 2 ml of saline. No further eating or drinking was permitted until after the conclusion of the test.

Human serum albumin macroaggregates 0.1 mg (Sorin Biomedica) labelled with 8MBq 99m Technetium were incorporated in the eggs during cooking. This radiopharmaceutical is not absorbed from the gut and is nonreactive to hepatitis B surface antigens.

Gastric emptying rate was measured by recording data from a gamma camera positioned over the stomach region, firstly for an anterior view and then for a posterior view. Initially recordings were made every 10 minutes and later every 30 minutes, and then at longer intervals for up to 7 hours after the drug administration.[2,3] In one patient, minimal reduction in activity in the stomach was seen at 7 hours and, regardless of the activity remaining, all studies were terminated at this time. Half-times for gastric emptying were calculated using the geometric mean of counts obtained from regions of interest around the stomach after allowing for decay of the isotope.[2]

Small intestinal transit time was measured in two ways. Firstly, the appearance of radioactivity over the surface of the caecum was assessed in the region of a point 2 cm medial to the anterior superior iliac spine. If intestinal transit was not complete by 7 hours, this time was taken as the transit time. Secondly, baked beans contain natural unabsorbable carbohydrates, stachyose and raffinose, which are metabolised by colonic bacteria which release hydrogen. This hydrogen is then absorbed into the bloodstream and can be detected in the exhaled breath,[4] so marking gastro-ileal transit time. Samples of air were collected at the end of a prolonged expiration every 20 minutes throughout the study, by aspiration into a 30-ml plastic syringe from the side arm of a modified Haldane–Priestley tube.[4] Breath hydrogen concentration was immediately measured with a hydrogen monitor (G.M.I. Medical Ltd).[5] The apparatus was calibrated frequently with a standard hydrogen gas concentration of 96 p.p.m. in air. Smoking was avoided throughout the study because it can result in spuriously high concentrations of hydrogen[6] in the breath.

Results

Three patients vomited, one after nalbuphine 10 mg and the two others after morphine 5 mg. Measurements could not continue. The other experimental results were used in Fig. 4 and Table 3.

Patient data are presented in Table 1. Figure 1 shows scintigraphs of the abdomen in a typical volunteer after morphine 5 mg and nalbuphine 10 mg.

Of the 10 volunteers who received nalbuphine 10 mg, two had gastric emptying half-times and five had small intestinal transit times longer than the maximum study period of 7 hours. This did not occur with the other injections. Figures 2 and 3 show the gastric emptying and intestinal transit results as cumulative graphs of each

Table 1. Sex distribution and mean (SD) age and weight of volunteers.

	Test drug	Age, years	Weight, kg	Sex, M:F
Group 1 ($n = 5$)	Nalbuphine 10 mg and saline	25.0 (6.6)	65.4 (5.3)	3:2
Group 2 ($n = 5$)	Morphine 5 mg and saline	32.0 (10.5)	60.2 (6.9)	1:4
Group 3 ($n = 5$)	Nalbuphine 10 mg and morphine 5 mg	31.4 (4.4)	73.6 (9.4)	5:0
Group 4 ($n = 5$)	Nalbuphine 5 mg and morphine 5 mg	35.2 (11.6)	67.8 (6.9)	4:1

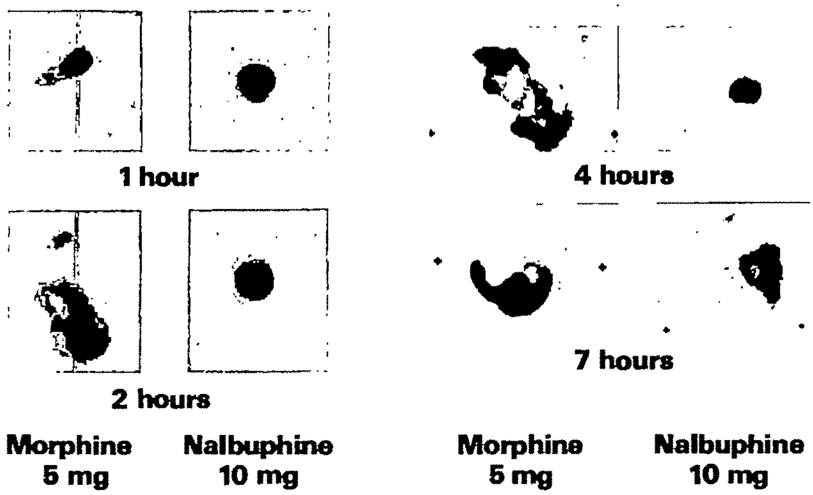

Fig. 1. The effect of nalbuphine 10 mg intravenously compared to morphine 5 mg intravenously on gastrointestinal motility. Gamma camera scans at 1, 2, 4 and 7 hours of the abdomen in the same volunteer in crossover study at one week interval. +, Anterior superior iliac crests.

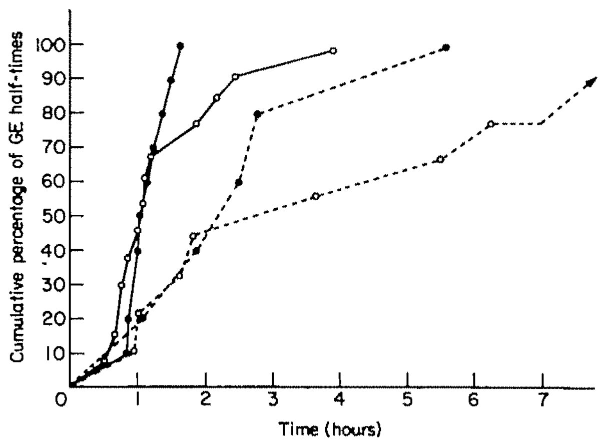

Fig. 2. Gastric emptying (GE) results as cumulative graphs of each individual time for each group. ●—●, Saline; O—O, morphine 5 mg; ● --- ●, nalbuphine 5 mg; O --- O, nalbuphine 10 mg.

individual time for each group. In Fig. 2, those who received placebo all had gastric emptying half-times of less than 2 hours. Twelve (80%) of those who had morphine 5 mg also did so, whereas only about one-third (five) of those who had nalbuphine 5 or 10 mg did so. Four (80%) of the nalbuphine 5 mg group had gastric emptying times of less than 3 hours, compared to 50% of those who had nalbuphine 10 mg. In Fig. 3, all small intestinal transit times were complete in those who had received the placebo by 4 hours, compared to 80% of those who had morphine 5 mg or nalbuphine 5 mg and 50% of those who had nalbuphine 10 mg. The patterns for morphine 5 mg and nalbuphine 5 mg are similar, whereas there is an obvious delay in those who had the higher dose of nalbuphine (10 mg).

The crossover experiments are compared within each group in Table 2. Gastric emptying

Table 2. Mean (SD) half-time for gastric emptying and small intestinal transit time.

	Half-time for gastric emptying, minutes	Small intestinal transit time, minutes	Statistical analysis by Student's paired *t*-test
Group 1 ($n = 4$)			
Nalbuphine 10 mg	198 (163)	305 (135)*	* $p < 0.05$ compared with placebo
Placebo	59 (12)	130 (12)	
Group 2 ($n = 4$)			
Morphine 5 mg	83 (46)	200 (107)*	* $p < 0.05$ compared with placebo
Placebo	79 (18)	160 (77)	
Group 3 ($n = 5$)			
Nalbuphine 10 mg	258 (164)*	330 (123)**	* $p < 0.05$
Morphine 5 mg	55 (9)	152 (41)	** $p < 0.01$ compared with morphine 5 mg
Group 4 ($n = 4$)			
Nalbuphine 5 mg	165 (119)*	245 (119)	* $p < 0.05$ compared with morphine 5 mg
Morphine 5 mg	122 (90)	215 (77)	

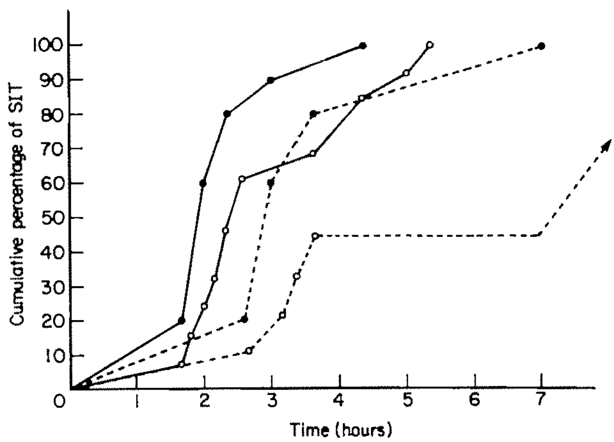

Fig. 3. Small intestinal transit time (SIT) results as cumulative graphs of each individual time for each group. ●—●, Saline; ○—○, morphine 5 mg; ●---●, nalbuphine 5 mg; ○---○, nalbuphine 10 mg.

was delayed after nalbuphine 10 mg compared with placebo ($0.05 < p < 0.1$), whereas there was no difference between gastric emptying with morphine 5 mg and with placebo. There were significantly longer gastric emptying half-times after both doses of nalbuphine than after morphine 5 mg; the higher dose of nalbuphine resulted in a greater delay. Morphine and nalbuphine both prolonged intestinal transit time compared to controls but there was little difference between morphine 5 mg and nalbuphine 5 mg while nalbuphine 10 mg resulted in a significantly longer transit time ($p < 0.01$).

Vomiting occurred in two (13%) of those volunteers (Table 3) who had morphine and in one (7%) of those who received nalbuphine. Nausea without vomiting was reported by six (40%) of those who had nalbuphine and in none who had morphine. Those who reported nausea had a highly significant prolongation in gastric emptying half-times and intestinal transit times (Table 4) compared to those who did not. The mean half-time of the former was about four times longer for those with nausea and the mean small intestinal transit time was at least twice as long (five experiments were limited, and ended at 7 hours). The three volunteers who vomited at 100, 185 and 285 minutes after drug administration had shown no sign of gastric emptying until that time.

Table 3. Side effects after intravenous nalbuphine and morphine.

	Group 1		Group 2		Group 3		Group 4	
	Nalbuphine 10 mg (n = 5)	Saline (n = 5)	Morphine 5 mg (n = 5)	Saline (n = 5)	Nalbuphine 10 mg (n = 5)	Morphine 5 mg (n = 5)	Nalbuphine 5 mg (n = 5)	Morphine 5 mg (n = 5)
No side effects		5	2	4	1	3	1	3
Nausea without vomiting	2				3		1	
Vomiting	1		1					1
Sweating	1				2		1	
Cold							1	
Flushed	1				2		1	1
Itching	1		1	1	1			
Sleepy	4		2		2	1	2	
Light-headed								1
Dizzy	4		1		3	1	2	2
Euphoric						1		1
Headache	1		1		1			

Table 4. Sex distribution and mean (SD) age, weight, half-time for gastric emptying and small intestinal transit time of five volunteers given nalbuphine 10 mg intravenously who had nausea and four volunteers given nalbuphine 10 mg intravenously who did not.

	Sex, M:F	Age, years	Weight, kg	Half-time for gastric emptying, minutes	Small intestinal transit time, minutes
Nausea after nalbuphine 10 mg (n = 5)	4:1	30.8 (7.0)	71.8 (9.6)	353 (83)**	420 (0)**
No nausea after nalbuphine 10 mg (n = 4)	4:0	26.8 (4.2)	69.8 (3.9)	79 (26)	192 (27)

** $p < 0.01$ compared with no nausea group (Student's unpaired t-test).

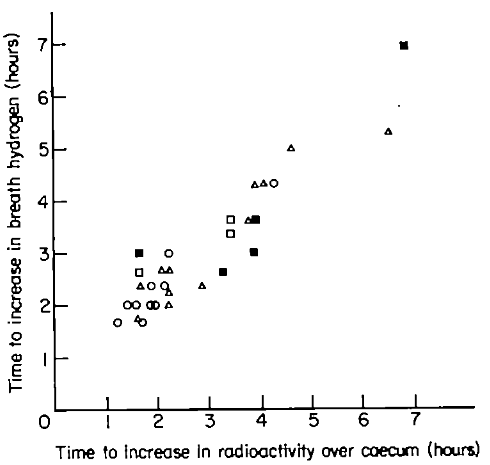

Fig. 4. Correlation (r = 0.934, $p < 0.001$) between the time for ingestion until the increase in radioactivity over the caecum, and the time until the increase in breath hydrogen. ○, Saline; △, morphine 5 mg; ■, nalbuphine 5 mg; □, nalbuphine 10 mg.

No increase in breath hydrogen occurred during either study in one volunteer in group 3, although caecal radioactivity appeared at 105 minutes after morphine 5 mg and at 190 minutes after nalbuphine 10 mg. The reason for this discrepancy is not apparent. In this case, the small intestinal transit time was determined from the increase in radioactivity over the caecum only. In the remaining 19 volunteers, there is a highly significant correlation between the time from ingestion until the increase in radioactivity over the caecum, and the time until the increase in breath hydrogen (r = 0.934, $p < 0.001$, Fig. 4).

Discussion

Both drugs caused prolongation of gastric emptying and small intestinal transit. It is apparent that nalbuphine 10 mg produces more depression of both these times than 5 mg, which

causes a similar delay to morphine 5 mg. This potency ratio of 1:1 is similar to that recommended for the analgesic effects,[1] although more recent work indicates that nalbuphine is less potent (by a factor of 1.2) than morphine.[7] If so, then it might be assumed that nalbuphine would have a longer duration of effect on the gut than an equivalent analgesic dose of morphine. However, this conclusion would not be justified, since the actual relation will be established only by a dose–response study of both drugs over a wider range of doses.

The findings here were unexpected since a previous study[8] indicated that nalbuphine 0.2–0.3 mg/kg produced less depression of the time to first flatus, a measure of coordinated bowel function, than did a lower dose of morphine, 0.15–0.2 mg/kg. However, these drugs were administered intramuscularly, not intravenously, and at a different dose, both of which factors could result in different effects. In the present study morphine 5 mg hardly delayed gastric emptying compared to placebo. In another study on volunteers, morphine 4–6 mg intravenously produced more rapid emptying of barium than no drug,[9] although other workers found that morphine 7.5 mg intravenously in volunteers delayed gastric emptying by 40%.[10] Morphine 10 mg doubled gastric emptying time, compared to placebo when tested 90 minutes after intramuscular administration.[11] These experiments probably indicate a trend towards increased depressant action on gastric emptying at higher doses of morphine. In animals, vomiting occurred less frequently after intravenous morphine than by other routes[12] and it was concluded that higher blood concentrations after intravenous administration depressed the vomiting centre.[13] Therefore, the intravenous route may also have been responsible, as well as dose differences, for the differing effects on gastrointestinal function found in this study compared to our previous report.[8]

Nausea induced by caloric vestibular stimulation or fear, inhibited gastric contractions in three volunteers and in one patient with a gastric fistula.[14] However, other workers did not accept that the motor function of the stomach can be used as a test of the effects of drugs on nausea.[15] In our study, there is a clear-cut relationship between nausea and vomiting and gastric and small intestinal delay which was exemplified in the higher dose patients. It would seem, therefore, that a report of nausea may be a good indication of such delay, and it would be worth exploring this relationship further with higher dose levels of morphine and other drugs.

The use of the gamma camera is the most accurate means of measuring gastric emptying and small intestinal transit times but is expensive and requires a dedicated data processor. The effect of drugs on gastric emptying can also be conveniently measured by paracetamol uptake.[16] Small intestine transit in this study showed such a good relationship between the two methods that, since it is more convenient, the breath hydrogen test will be employed for future drug studies despite its one failure. A study of gastric emptying and intestinal transit that combined paracetamol uptake and breath hydrogen tests, would require a minimum of special facilities. This study shows the important and complex effects of opioid drugs on gastrointestinal function. Therefore, there is a need for further systematic studies over a range of doses and routes.

The differences between morphine 5 mg, nalbuphine 5 mg and placebo were not large. The longer delays occurred with the larger dose of nalbuphine, as did most of the instances of nausea and vomiting. This suggests a dose-dependent effect. This could be important and suggests the use of smaller repeated doses, perhaps by patient-controlled analgesia, rather than the larger intramuscular dose administered currently. This measure might prevent some postoperative discomfort.

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The respiratory effects of isoflurane, enflurane and halothane in spontaneously breathing children

I. MURAT, M. CHAUSSAIN, J. HAMZA AND CL. SAINT-MAURICE

Summary

The respiratory effects of halothane, isoflurane and enflurane were assessed during nitrous oxide anaesthesia (N_2O 50%) in three groups of unstimulated, spontaneously breathing children who weighed 10–20 kg and were aged 1–6 years. Respiratory variables were measured or calculated from capnographic and pneumotachographic recordings at three multiples of minimal alveolar concentration (MAC). The slope of the carbon dioxide response was measured. Similar increases in end tidal carbon dioxide were found for the three agents at each MAC multiple, and similar decreases in tidal volume and in the slope of the ventilatory response to carbon dioxide. A dose-related tachypnoea occurred with halothane and a significant decrease in the duration of inspiration and the duration of each breath at the deepest level of anaesthesia. A significant increase in both these times occurred with enflurane, and a decrease in respiratory rate. No change in respiratory rate occurred with isoflurane at increasing alveolar concentrations whereas at each level of anaesthesia inspiratory time was significantly reduced.

Key words

Anaesthetic agents; halothane, isoflurane, enflurane.
Anaesthesia; paediatric.

Inhalational agents are widely used in paediatric anaesthesia for both induction and maintenance of general anaesthesia. Halothane is the most commonly used agent in paediatric anaesthesia but the other two have specific advantages. Enflurane is used extensively for ear, nose and throat surgery in order to reduce the incidence of cardiac dysrhythmias.[1,2] The most recently introduced agent, isoflurane, has fewer risks of hepatic toxicity and fewer adverse cardiovascular effects.[3] However, the effects of each agent on respiratory patterns are of major clinical relevance because children are allowed to breathe spontaneously during short surgical procedures. In a previous study,[4] we reported that in young children isoflurane and halothane had similar respiratory effects up to 1.1 × minimal alveolar concentration (MAC), although isoflurane produced a more marked decrease in minute ventilation at deeper levels of anaesthesia, owing to a lesser increase in respiratory frequency when compared with halothane. Enflurane also differs from halothane as regards its effects on respiratory frequency[5,6]

I. Murat, MD, Departement d'Anesthésie Réanimation Chirurgicale, M. Chaussain, MD, Laboratoire d'Epreuves Fonctionnelles Respiratoires, J. Hamza, MD, Cl. Saint-Maurice, MD, Departement d'Anesthésie Réanimation Chirurgicale, Hopital Saint Vincent de Paul, 74 Avenue Denfert, Rochereau 75674, Paris, Cedex 14, France.
Correspondence should be addressed to Dr I. Murat please.

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but no precise study has compared the three halogenated agents at the same MAC multiples in children.

Material and methods

The respiratory effects of halothane (group 1), isoflurane (group 2) and enflurane (group 3) were assessed during nitrous oxide anaesthesia in three groups of children aged 1–6 years. All the children were classified as ASA grade 1, were taking no medication and were free from cardiac and respiratory diseases. All were scheduled for elective genito-urinary or orthopaedic surgical procedures (hypospadias repair, club foot correction, surgery of external genital organs). None was premedicated. Informed parental consent was obtained during the pre-operative visit, as was the approval of the hospital ethical committee.

Induction of anaesthesia was carried out with one of the three agents in a mixture of 50% oxygen and nitrous oxide, and tracheal intubation was performed without muscle relaxant or opiates. The children were then allowed to breathe spontaneously through an open system with a non-rebreathing, low-opening-pressure valve (Digby–Leigh).

In groups 1 and 2 the respiratory studies were carried out before the surgical procedure and the children were not stimulated. In group 3, after tracheal intubation, an epidural anaesthetic was established. The puncture was made using a Tuohy 18- or 19-G needle at L_{4-5} or L_{3-4} and, after insertion of an epidural catheter, a dose of 0.75 ml/kg bupivacaine 0.25% with adrenaline 1:200 000 was injected. All respiratory and haemodynamic variables were recorded and respiratory studies were undertaken if no changes in the above variables occurred at skin incision. Mean time of skin incision ranged between 25 and 30 minutes and, during this interval, children were maintained at the lowest level of anaesthesia considered in the present study (0.8 MAC).

In each group, three levels of anaesthesia were successively studied in the same order: 0.8 MAC, 1.1 MAC and 1.4 MAC. The expiratory fraction of each agent was measured using an infrared analyser (Normac, Datex). MAC multiples were calculated assuming the contribution of 50% nitrous oxide to be 0.5 MAC. MAC for each agent was corrected for age. For children aged between 1 and 6, MAC for halothane is 0.91[7] and MAC for isoflurane is 1.6.[8] The exact MAC of enflurane has not yet been determined in young children. The recommendations of laboratory and paediatric anaesthesia textbooks, suggest that MAC for enflurane for this age group should be considered to be 2%.

Measurements

The concentration of expired carbon dioxide was measured continuously throughout the study by capnograph (Datex) with automatic correction for nitrous oxide. The rate of sampling was 50 ml/minute. Samples were obtained directly from the proximal end of the tracheal tube. The carbon dioxide waveform was recorded continuously and the presence of an end tidal plateau was verified for all patients.

Inspired gas flow was measured with a Fleisch heated pneumotachograph Model 1/0 (Gould) connected to a differential pressure transducer (Godart). The pneumotachograph head was inserted between the non-rebreathing valve and the tracheal tube. The flow signal was calibrated before each study with the flow calibration set (Godart). The tidal volume (V_T) was derived by electronic integration of the inspiratory flow signal.

Tidal volume was calibrated before and after each study with room air using syringes of known volume (60 ml). The temperature of room air used for the calibration ranged between 24 and 26°C and was not different from the temperature of the inspired gas mixture used. Tidal volume was recorded throughout the study on a twin-channel, rapid response recorder (Gould–Godart).

The following variables were then measured manually by averaging 10 successive breaths recorded at a chart speed of 750 mm/minute in the steady state: inspiratory time (T_I), total respiratory time (T_{TOT}) and respiratory frequency (f). The following variables were calculated: mean inspiratory flow $\dot{V}_I$ (ml/minute/kg), effective inspiratory time (T_I/T_{TOT}) and end tidal carbon dioxide partial pressure ($P_{E'}CO_2$, kPa). $\dot{V}_E$, V_T and $\dot{V}_I$ were corrected to body temperature and pressure saturated (BTPS).

Baseline ventilatory measurements were obtained at a selected MAC for each agent, and carbon dioxide was then added to the inspired gas mixture so as to produce a constant inspir-

atory carbon dioxide concentration of 2% indicated by the capnograph. This value was chosen in order to produce a moderate increase in $P\text{E}'\text{CO}_2$ but within the physiological range.

Measurements of ventilation were made after 5 minutes at a given inspired carbon dioxide concentration, when the patients were considered to be in a steady state, although in all patients the respiratory variables were stable within 2 minutes of achieving the desired inspired concentration of carbon dioxide. The slope of $\Delta\dot{V}\text{E}/\Delta P\text{E}'\text{CO}_2$ (ml/minute/kg/kPa) was used to express the sensitivity to carbon dioxide.

Statistical analysis

Statistical analyses were made using a one-way analysis of variance for comparison between groups and then Student's *t*-test for unpaired data. Comparisons in the same group of children were made using analysis of variance and Student's *t*-test for paired data.

Results are expressed as mean (SEM). Values of p of 0.05 or less, are regarded as significant.

Results

The characteristics of the population are shown in Table 1. The three groups of children were of similar age, weight and height. Results of statistical analyses in the same group are indicated in Table 2. Significant changes between groups are shown in Figs 1–5.

The respiratory variables measured for the three agents at 0.8 MAC differ only as concerns *T*I and *T*I/*T*TOT. *T*I was shorter with isoflurane, and *T*I/*T*TOT was significantly less, compared with group 1 ($p < 0.01$) or group 3 ($p < 0.01$). No other significant difference was found between the three agents.

Table 1. Population data: values expressed as mean (SEM).

	Group 3 (enflurane)	Group 2 (isoflurane)	Group 1 (halothane)	p
n	9	10	10	—
Mean (SEM) age, months	43.8 (4.0)	46.2 (4.2)	45 (4.7)	NS
Mean (SEM) height, cm	96.6 (3.7)	103.5 (2.5)	99.9 (2.7)	NS
Mean (SEM) weight, kg	13.8 (1.0)	16.1 (0.7)	15.9 (0.8)	NS

Table 2. Mean values (SEM) for $P\text{E}'\text{CO}_2$ (kPa), *V*T (ml/kg), $\dot{V}$I, $\dot{V}$E (ml/kg/minute), *f* and *T*I/*T*TOT obtained for each group at different levels of anaesthesia (MAC multiples 0.8, 1.1, 1.4).

	0.8 MAC			1.1 MAC			1.4 MAC		
	Group 3	Group 2	Group 1	Group 3	Group 2	Group 1	Group 3	Group 2	Group 1
$P\text{E}'\text{CO}_2$	4.56	5.09	5.14	5.08	5.5	5.46	5.65	6.46	6.09
	(0.34)	(0.13)	(0.22)	(0.41)*	(0.11)***	(0.25)***	(0.58)*	(0.14)***	(0.27)***
*V*T	5.6	4.86	4.86	4.72	3.72	4.01	3.68	2.83	3.29
	(0.3)	(0.5)	(0.4)	(0.18)**	(0.4)***	(0.34)***	(0.18)***	(0.36)***	(0.34)***
*T*I	1.31	0.92	1.1	1.51	0.88	1.04	1.53	0.89	0.95
	(0.11)	(0.07)	(0.11)	(0.09)	(0.05)	(0.1)	(0.05)*	(0.06)	(0.09)**
*T*TOT	2.4	2.12	2.03	2.53	2.07	1.94	2.61	2.07	1.8
	(0.14)	(0.15)	(0.16)	(0.15)	(0.19)	(0.16)	(0.13)**	(0.23)	(0.15)**
$\dot{V}$I	271.6	315.6	272	192.2	258.9	240.1	144.6	192.7	212.5
	(26.4)	(26.6)	(14.9)	(11.0)**	(26.4)***	(16.9)***	(6.5)***	(20.1)***	(12.1)***
*T*I/*T*TOT	0.54	0.44	0.54	0.59	0.44	0.53	0.59	0.45	0.52
	(0.03)	(0.02)	(0.02)	(0.01)	(0.03)	(0.01)	(0.01)	(0.03)	(0.01)
f	25.7	29.7	31.7	24.4	30.7	33.05	23.5	31.7	35.7
	(1.7)	(2.2)	(3.0)	(1.5)	(2.5)	(2.9)	(1.25)*	(3.0)	(3.2)***
$\dot{V}$E	142.2	135.8	145.9	114.4	107.9	127.3	85.3	82.7	111.9
	(8.7)	(9.6)	(7.6)	(6.0)***	(9.2)***	(9.1)***	(4.4)***	(7.9)***	(7.0)***
Slope	15.3	15.4	16.1	8.2	6.7	7.1	4.7	3.3	4.5
	(3.1)	(2.5)	(1.9)	(1.7)*	(1.3)***	(0.9)***	(1.4)**	(0.5)***	(1.2)***

Significant changes for each group with increasing alveolar fraction of each agent are indicated as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The slope of the carbon dioxide response is expressed in ml/minute/kg/kPa.

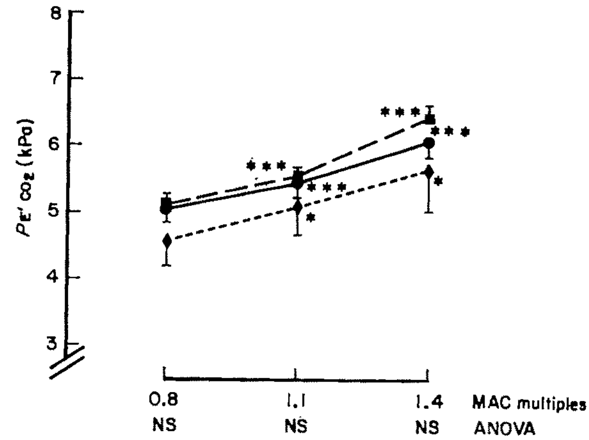

Fig. 1. Changes in $P_{E'}CO_2$ (kPa) in each group with increasing alveolar fraction of each agent. Comparisons for each agent against value at 0.8 MAC are indicated as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Comparisons between groups at each MAC multiple are indicated at the bottom (analysis of variance). ●, Halothane; ◆, enflurane; ■, isoflurane.

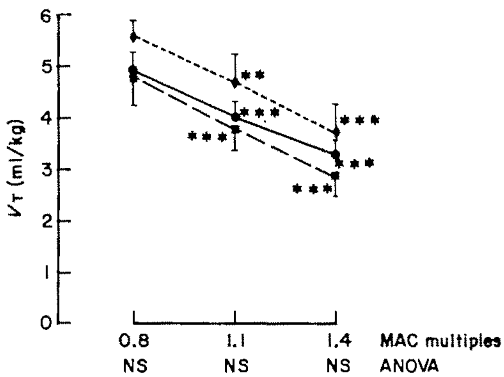

Fig. 2. Changes in tidal volume. For legend, see Fig. 1.

A similar increase was found for $P_{E'}CO_2$ at 1.1 MAC, and a similar decrease in V_T. The effects of the three agents on respiratory frequency obviously differ. Respiratory frequency was significantly less in group 3 and T_I was significantly longer in group 3 ($p < 0.001$ vs group 2, $p < 0.01$ vs group 1). T_I/T_{TOT} was significantly different among the three agents ($p < 0.01$ group 2 vs group 3, $p < 0.05$ group 2 vs group 1 and $p < 0.02$ group 1 vs group 3). Despite significant differences in frequency f, none was found for $\dot{V}_E$ or $\dot{V}_I$ at this level of anaesthesia. There were no significant changes in the slope of the carbon dioxide response between the three agents.

No significant difference was observed either for $P_{E'}CO_2$ or for V_T between the three agents at 1.4 MAC. However, significant differences were observed in respiratory frequency. In group 3, the respiratory frequency was significantly reduced compared to that in group 1 or group 2. No significant difference was observed between groups 1 and 2. In group 3, the duration of inspiration was significantly longer when compared to both group 1 ($p < 0.001$) and group 2 ($p < 0.001$). The same differences for T_I/T_{TOT} were observed as described at 1.1 MAC. At this level of anaesthesia, $\dot{V}_E$ was significantly less reduced with halothane, when compared to both group 3 and group 2. The inspiratory flow rate $\dot{V}_I$ was significantly lower under enflurane when compared to both group 1 and group 2. No significant difference was observed between groups 1 and 2. The slope of the carbon dioxide response decreased similarly in the three groups. Changes in $\dot{V}_E$ during inhalation of carbon dioxide are due solely to changes in tidal volume without change in respiratory timing at each MAC level.

Discussion

Methods

Groups 1 and 2 were studied before the surgical procedures whilst the third group was studied

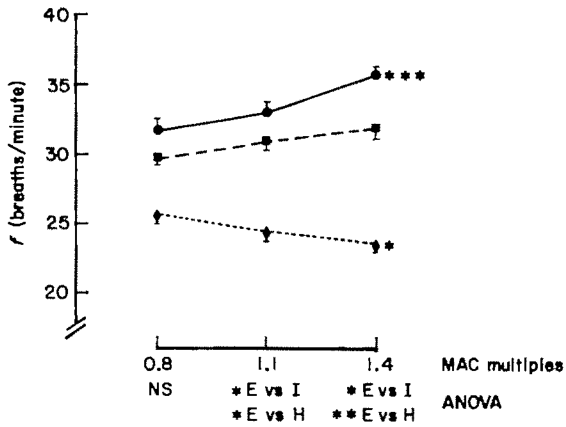

Fig. 3. Changes in respiratory frequency. For legend, see Fig. 1.

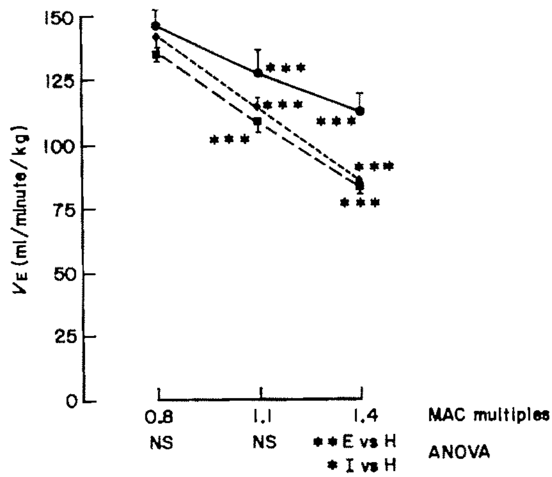

Fig. 4. Changes in minute ventilation. For legend, see Fig. 1.

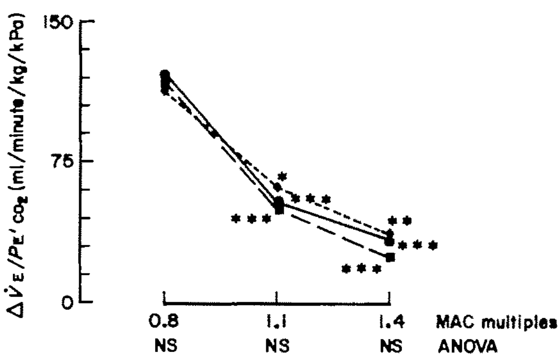

Fig. 5. Changes in slope of ventilatory response to carbon dioxide, $\Delta\dot{V}_E/\Delta P_E'CO_2$ (ml/minute/kg/kPa). For legend, see Fig. 1.

during the surgical procedure but with additional epidural anaesthesia. We considered that the children in group 3 were not stimulated during the surgical procedure, since no change in the haemodynamic or ventilatory variables was observed at the time of the skin incision. The upper level of blockade in this group was lower than T_{10} in all cases and thus did not affect respiratory function. Furthermore, the concentration of bupivacaine used (0.25%) does not generally produce clinical evidence of motor blockade. A possible direct ventilatory effect of bupivacaine itself cannot be ruled out. In fact, a direct stimulating ventilatory effect of lignocaine was recently reported after either an intravenous infusion or an epidural injection[9] but no such effect has been reported up to now with bupivacaine.

The MAC multiples defined in the present study may be subject to criticism for two main reasons. The first is the absence of precise determination of the MAC of enflurane in children of this age group. The second is that the alveolar fraction of halogenated agents may be underestimated using the Normac analyser when the respiratory frequency is greater than 24 breaths/minute.[10,11] Both halothane and isoflurane anaesthesia were associated with respiratory rates greater than 24 breaths/minute and so the concentrations measured may be underestimated for these two agents. However, the inspired concentrations of each agent necessary to achieve these three levels were widely different in each group studied and so, at least, they represent three clinical levels of anaesthesia: light level below 1 MAC, medium level around 1 MAC, deep level above 1 MAC, even if they are not precise MAC multiples.

Comparative respiratory effects

At the light level of anaesthesia, no significant change between groups was found for $\dot{V}_E$ or $P_{E'}CO_2$ nor for V_T or f. When compared to normal resting values of respiratory variables in unanaesthetised children of this age group,[12] $\dot{V}_E$ was within the normal range in the three groups, and respiratory rate was increased in both groups 1 and 2 and near to normal in group 3. Inspiratory time was significantly shorter with isoflurane when compared to that with the other agents. This could be related to the respiratory responses which occurred during induction of anaesthesia in half of the children in group 2 (coughing in five children with minor laryngospasm in two). None of these occurred in the other groups. The group 2 patients who did not present respiratory problems during induction of anaesthesia, had a slower respiratory rate and a longer T_I than the others. However, the changes between patients were not significant, owing to the small number of children. In anaesthetised dogs, Savoy[13] reported that ventilatory drive adaptation to bronchospasm does not require the animal to be conscious. The breathing pattern in response to bronchospasm consisted of tachypnoea associated with decreased V_T, decreased T_I and unchanged V_I. These changes seem to be due to an increase of vagal activity. Induction using isoflurane is often associated with respiratory responses in children,[14,15] from an irritant effect on the upper airways. Adequate premedication could have reduced the respiratory effects observed in the present study.

With increasing depth of anaesthesia, the main difference between the three agents is the effect on respiratory rate. Enflurane anaesthesia is associated with a lower, near to normal, respiratory rate and halothane with a marked tachypnoea. $P_{E'}CO_2$ was increased identically in the three groups. These results are different from those reported in adults, where enflurane seems to have a greater respiratory depressant effect than the other two agents.[3,16,17] The MAC multiples in both groups 1 and 2 may be greater than those obtained with enflurane because of the technical characteristics of the Normac analyser.[10,11] However, the same decrease in the slope of the carbon dioxide response accounts for a similar central respiratory depressant effect of the three agents at the MAC multiples studied. At 1.4 MAC, halothane reduces minute ventilation less than the other two agents. The lack of difference in the $P_{E'}CO_2$ values observed at 1.4 MAC may result from a relative increase in wasted ventilation in group 1 and, to a lesser extent, in group 2, or from reduced carbon dioxide production in group 3, due to partial motor block.[18] The effect of apparatus deadspace in children may lead to error in the conclusions. It can only be presumed that a smaller apparatus deadspace, as used in clinical practice, may result in the clearest evidence of the reduced ventilatory depressant effect of halothane in children at the deepest level of anaesthesia.

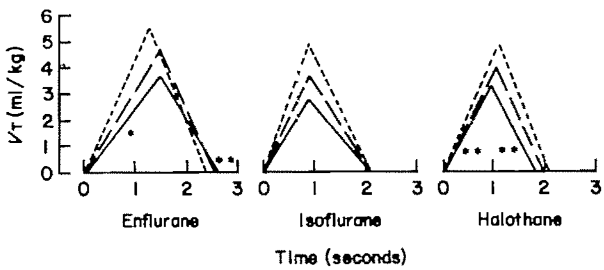

Fig. 6. Changes in breathing patterns (*T*I, *T*TOT, *V*T) for each agent at three different MAC multiples. – – – –, 0.8 MAC; — —, 1.1 MAC; ——, 1.4 MAC. Comparisons with the changes in *T*I and *T*E at 1.4 MAC versus 0.8 MAC are indicated as follows: *$p < 0.05$. **$p < 0.01$.

Changes in breathing patterns were very different with the three halogenated agents (Fig. 6). The changes in breathing pattern in the present study were identical to those reported in adult studies,[5,6] despite a higher respiratory rate in young children at rest when compared to adults. The major differences in respiratory waveforms between halothane and enflurane anaesthesia were a longer inspiratory time, a longer respiratory cycle time and a lower mean inspiratory flow in group 3.

The carbon dioxide response decreased identically at each level of anaesthesia with the three agents. The same results have been reported in adults.[19] However, when compared with normal values published for awake neonates, adolescents or adults,[19–21] the slope of the carbon dioxide response is obviously decreased even at a light level of anaesthesia. The addition of carbon dioxide produces solely an increase of *V*T, without changes in respiratory rate. In all available studies, in both adults and children, it seems that changes in $P\text{E}'CO_2$ have little influence on respiratory frequency whichever agent is used.

Conclusion

In children, enflurane, halothane and isoflurane produce a similar decrease in tidal volume with increasing depth of anaesthesia. However, the effects of the three agents on respiratory rate and breathing patterns obviously differ. Enflurane is associated with a slower, near to normal, respiratory rate and halothane with a marked tachypnoea. The net result is that halothane reduces minute volume ventilation less than the two other agents at the deepest level of anaesthesia studied. The respiratory effects which occur during induction of anaesthesia, as observed with isoflurane, may affect the respiratory patterns for a prolonged period after induction.

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Peak intratracheal pressure during controlled ventilation in infants and children

A computer study of the Servo 900C ventilator

A. SYNNOTT, W. S. WREN AND J. DAVENPORT

Summary

The mathematical relationship between peak ventilator breathing system pressure displayed on the digital meter of the Siemens SV900C ventilator, and peak intratracheal pressure measured at the distal end of the tracheal tube, was defined and incorporated into a computer program. The mean difference between peak airway pressure calculated by the computer and directly measured peak intratracheal pressure was 0.02 kPa (SD 0.10) in 18 infants and children. The mean difference between ventilator breathing system pressure and intratracheal pressure in the same group was 0.82 kPa (SD 0.91). Bench tests established that the decrease in peak pressure displayed by the ventilator (from 1.36 to 0.38 kPa) while inspiratory time was increased from 20 to 80% of the respiratory period, concealed an increase (from 0.2 to 0.38 kPa) in intratracheal pressure which occurs during this process; and that the large increase in pressure displayed by the ventilator (from 0.3 to 6 kPa) while respiratory frequency was increased from 20 to 120 breaths/minute, concealed a small increase in peak intratracheal pressure (0.2–0.3 kPa) which occurs during this process. These changes were accurately predicted by the computer program. The increase in intratracheal pressure associated with prolonged inspiratory times explains the high incidence of barotrauma which has recently been associated with this procedure in infants.

Key words

Anaesthesia; paediatric.
Ventilation; airway pressure.

The contribution of high peak airway pressures to the incidence of pulmonary barotrauma in infants during intermittent positive pressure ventilation of the lungs (IPPV) is generally acknowledged[1–4] and some workers have attempted to define the peak airway pressures which can be used with safety in such conditions as respiratory distress syndrome.[5] Attempts to reduce the incidence of these complications have devolved on two principal approaches: the application of prolonged inspiratory time and reversed inspiratory/expiratory (I/E) ratios,[5] and the use of high frequency positive pressure ventilation (HFPPV),[6] both of which are claimed to produce effective ventilation with lower mean and peak airway pressures than conventional IPPV. It is evident, therefore, that accurate knowledge of airway pressure at its effective site, the distal end of the tracheal tube, and the response of intratracheal pressure to alterations in the pattern of ventilation, could make a significant contribution to the understanding and management of ventila-

A. Synnott, MB, FFARCSI, Research Fellow, W.S. Wren, MB, FFARCSI, FFARCS, Consultant, J. Davenport, Electronics Technician, Department of Anaesthetics, Our Lady's Hospital for Sick Children, Dublin 12, Ireland.

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tion in infants. However, as has been appreciated for some time,[7,8] there is a considerable gradient between pressures recorded by the ventilator and the pressures at the distal end of the tracheal tube. This gradient may be highly variable, depending upon the site at which the ventilator records breathing system pressure; thus, many ventilator displays give inaccurate, and often seriously misleading, information about airway pressure.

The advent of the Servo 900C (Siemens) ventilator, which provides a digital reading of pressure in the expiratory limb proximal to the ventilator, suggested that it should be possible to quantify the relationship between ventilator breathing system pressure and intratracheal pressure, which can be measured accurately at the distal end of the tracheal tube even in small infants.[8] It should then be possible to define correction factors by which intratracheal pressure could be derived from ventilator breathing system pressure, and avoid the requirement for complex calculations in clinical practice by incorporating these factors in a computer program. Furthermore, the program should be capable of prediction of the effects of alterations in the respiratory pattern on intratracheal pressure, and thereby avoid the need to introduce changes in the respiratory pattern on a trial-and-error basis.

In order to calculate intratracheal pressure, it is essential that the ventilator manometer is intrinsically accurate. Ideally, it should measure pressure at the proximal end of the tracheal tube but measurement in the expiratory limb of the system proximal to the ventilator is acceptable provided the compressible volume of the ventilator breathing system is minimal. Measurement at the inspiratory outlet, though possible in principle, makes the calculations more difficult because errors due to flow through the inspiratory limb and the compressible volume of the humidifier must be taken into account.

The other essential requirement is that the inspiratory flow rate at the moment of occurrence of peak airway pressure, is known. In true constant flow generators this can be calculated by dividing the inspiration time into the inspired tidal volume. The alternative is to use a ventilator equipped with an inspiratory flow transducer whose output is available in machine readable form, and interface it directly with a computer which calculates the correction factors. This approach is more accurate and is applicable to all modes of ventilation, such as pressure supported ventilation, pressure limited ventilation and intermittent mandatory ventilation (IMV), and allows automatic presentation, in real time, of fully corrected airway pressure data to the clinician.

Methods

These possibilities were investigated in a study which consisted of a series of bench tests: to establish the accuracy of the ventilator's digital meter; to measure the pressure gradient due to the compressible volume of the expiratory limb of the ventilator breathing system; to measure the pressure gradient due to flow through the tracheal tube; to compare the effects of alteration in inspiratory time on intratracheal pressure and pressure recorded by the ventilator's digital meter; and to compare the effects of alterations in respiratory frequency on intratracheal pressure and pressures recorded by the ventilator's digital meter.

A series of pressure measurements were also made at the distal end of the tracheal tube in infants and children, to provide accurate clinical data for comparison with the bench tests and to test the accuracy of the computer program devised from them.

Bench tests

The equipment used in the tests was as follows. The standard paediatric tubing for the ventilator, with a heated humidifier (Ohio) included in the inspiratory limb, was connected to a test lung (Bennett) via a paediatric swivel mount and a range of tracheal tube sizes with their matched connectors (Portex). Pressures at the ventilator end of the expiratory limb and at both proximal and distal ends of the tracheal tube were measured, using a short piece of narrow bore, thick walled tubing connected to the pressure channel of a Mercury VP5 ventilator/pump test meter. The pressure channel of this instrument has a frequency response of 0–11 Hz and is therefore capable of accurate measurement of the pressure changes throughout the full range of frequency produced by the ventilator (0–120 breaths/minute). This instrument was calibrated using a water manometer and, to facilitate accurate measurement and recording, its analogue output

was fed via an analogue-to-digital converter into a computer. A pneumotachograph (Fleisch II) was inserted into the inspiratory limb and connected to the differential pressure transducer of the VP5 to provide data on flow and, by integration, volume. The pneumotachograph was calibrated using calibrated flow meters (Fisher) for the flow channel and syringes of known volume (Hamilton) for the volume channel. In both tests the ventilator was used in its volume controlled mode, with a constant inspiratory flow pattern. The accuracy of the digital meter of the ventilator (test a) was assessed in three Servo 900C ventilators which had been calibrated and tested according to the manufacturer's instructions prior to the study. In test b, the pressure gradient due to the compressible volume of the expiratory limb of the ventilator breathing system was assessed in a series of 95 paired readings of pressure recorded at the proximal end of the tracheal tube, measured by the Mercury VP5, and at the proximal end of the expiratory breathing tube, measured by the Servo 900C. Measurements were recorded for a range of respiratory frequencies, 20–120 breaths/minute with tidal volumes ranging from 30 to 300 ml, and a range of tracheal tubes from 3.0 to 7.0 mm internal diameter.

Pressure gradients due to flow through the tracheal tube (test c) were measured for the full range of tracheal tube sizes (2–10 mm internal diameter) with air flow rates that ranged from 0 to 1.7 litres/second for each. Flow rates were measured with calibrated flow meters (Fisher). The pressure gradients produced by flow through the orifice of the tracheal tube connector alone, and flow through the complete tracheal tube and connector, were measured with the Mercury VP5 ventilator/pump test meter. The results were plotted on a graph of ln(pressure gradient) against ln(flow) and the equation of the resulting best-fit lines was determined using linear regression analysis.

The effect of prolonging inspiratory time (test d) from 20 to 80% of the respiratory period, with a constant respiratory frequency of 40 breaths/minute and constant tidal volume (V_T) of 50 ml, was assessed in a series of 100 paired readings of peak pressure recorded at the distal end of a tracheal tube (3.0 mm internal diameter, 10 cm length) and the ventilator's digital meter. The effect of increasing respiratory frequency (test e) was assessed in a series of 100 paired readings of peak pressure recorded at the distal end of the same tracheal tube and the ventilator's digital meter, while the respiratory rate was increased from 20 to 120 breaths/minute with a constant V_T of 50 ml and inspiratory/expiratory time ratio of 1/3.

Clinical data

A sequence of 23 airway pressure measurements were performed in 18 infants and children, whose clinical data and indications for ventilation are presented in Table 1. The Servo 900C ventilator was used in all cases. Intratracheal pressure was measured by means of a specially constructed tracheal tube with a manometer tube incorporated in its wall (Portex). The proximal end of the manometer tube was connected to the pressure channel of the Mercury VP5.

The peak intratracheal pressures recorded in the 18 patients and the peak pressures displayed by the ventilator's digital meter while these pressures were being recorded, were compared using the methods recently described by Bland and Altman.[9] The data displayed by the digital meter were then fed into the computer and the resulting calculated peak intratracheal pressures compared with the measured intratracheal pressures using the same methods. The factors employed in designing the program are described in the Appendix.

Results

Bench tests

The behaviour of the three Servo 900C ventilators was identical and there was no significant difference between pressures recorded by the digital meter and the pressure channel of the VP5 test meter.

The mean value of the error due to the compression volume in the expiratory limb of the ventilator was 0.07 kPa (SD 0.05). This was regarded as insignificant in the context of the much greater differences between true airway pressure and pressure registered by the ventilator.

Pressure gradients due to flow through the tracheal tube varied inversely with the diameter of the tube. Thus, for example, with a tube of 3.0 mm ID and 10 cm length, pressure gradients

Table 1. Details of patients from whom clinical data were derived.

Patient	Indication for ventilation	Age (days, except where stated)	Weight (kg)	Tracheal tube (mm ID)	Tidal volume (ml)	Respiratory rate (breaths/minute)	Inspiratory time (%)	Airway pressure (kPa)		
								Ventilator	Computer	True
1	Cardiac surgery	6 years	18	5.0	120	30	33	0.2	0.03	0.15
2	Pneumonia and croup	2 years	16	3.0	80	50	25	4.2	0.92	1.0
2	Pneumonia and croup	2 years	16	3.0	80	50	33	3.3	1.44	1.3
3	Postoperative	2	3.2	3.0	30	100	25	2.0	0.38	0.4
4	Tr-oes fistula	1	3.4	3.5	40	40	25	0.6	0.35	0.3
5	Cardiac surgery	3	3.3	3.0	30	60	25	1.2	0.63	0.6
5	Cardiac surgery	3	3.3	3.0	35	60	25	2.1	1.34	1.4
6	Cardiac surgery	9	3.8	3.5	40	35	25	1.4	1.21	1.2
7	Cardiac surgery	1 year	10	4.5	100	30	25	1.5	1.23	1.2
8	Respiratory distress syndrome	3	2.1	3.0	30	40	25	1.4	1.13	1.1
8	Respiratory distress syndrome	3	2.1	3.0	30	40	50	1.2	1.13	1.2
8	Respiratory distress syndrome	3	2.1	3.0	30	110	25	3.0	1.03	1.0
9	Cardiac surgery	6 years	22	6.0	200	20	25	0.9	0.75	0.5
10	Postoperative	1	3.7	3.5	40	40	33	1.0	0.9	0.9
11	Postoperative	2	3.6	3.5	35	50	25	0.7	0.42	0.6
12	Exomphalos	1	3.8	3.5	40	35	33	1.0	0.92	0.7
13	Respiratory distress syndrome	3	2.3	3.0	35	40	25	1.2	0.83	0.9
14	Fallot's tetralogy	1	3.4	3.5	35	40	25	1.1	0.91	0.9
15	Cardiac surgery	3 years	14	5.0	125	20	25	0.9	0.77	0.8
16	Cardiac surgery	1 year	9.5	4.5	100	30	25	1.3	1.02	0.9
17	Diaphragmatic hernia	2	3.3	3.0	30	100	25	2.0	0.38	0.4
17	Diaphragmatic hernia	2	3.3	3.0	35	100	25	2.8	0.58	0.6
18	Pneumonia	3	3.5	3.5	40	110	25	3.2	1.36	1.2

Table 2. Slope, intercept and correlation coefficient (r) from linear regression analysis of a scatterplot of ln(air flow rate, litres/second) (X axis) against ln(pressure gradient across orifice, kPa) (Y axis) for each size of Portex tracheal tube connector studied.

Orifice size	Slope	Intercept	r
2.0	1.934	3.906	0.996
2.5	1.967	3.251	0.999
3.0	2.043	2.887	0.999
3.5	1.956	2.277	0.999
4.0	2.075	1.903	0.999
4.5	2.062	1.219	0.999
5.0	2.058	0.878	0.999
5.5	1.984	0.422	0.999
6.0	2.071	0.084	0.999
6.5	2.094	−0.247	0.999
7.0	2.093	−0.541	0.998
7.5	2.123	−0.625	0.999
8.0	1.870	−1.130	0.999
8.5	1.870	−1.130	0.999
9.0	2.182	−1.627	0.999
9.5	2.182	−1.627	0.999
10.0	2.155	−1.989	0.997

Table 3. Slope, intercept and correlation coefficient (r) from linear regression analysis of a scatterplot of ln(air flow rate, litres/second) (X axis) against ln(pressure gradient/cm length of tube, kPa) (Y axis) for each size of Portex tracheal tube studied.

Tube size	Slope	Intercept	r
2.0	1.662	0.621	0.993
2.5	1.550	−0.415	0.993
3.0	1.431	−1.282	0.994
3.5	1.466	−1.889	0.990
4.0	1.407	−2.547	0.987
4.5	1.364	−3.025	0.984
5.0	1.573	−2.956	0.980
5.5	1.586	−3.246	0.994
6.0	1.572	−3.421	0.998
6.5	1.587	−3.813	0.999
7.0	1.414	−4.423	0.991
7.5	0.982	−5.681	0.993
8.0	1.337	−4.999	0.982
8.5	1.047	−5.876	0.987
9.0	1.336	−5.828	0.999
9.5	1.135	−6.557	0.999
10.0	1.432	−6.252	0.999

ranging from 0.1 to 1.4 kPa were recorded at flow rates of 0.05–0.25 litres/second, which are commonly used in IPPV in infants; while, with the same tube, pressure gradients of up to 6.2 kPa were recorded with flow rates of 0.5 litres/second, which are used during HFPPV with the Servo 900C in infants. In contrast, the pressure gradients recorded with a tube of 9.0 mm ID and 25 cm length with the flow rates used in adult IPPV (up to 1 litre/second), did not exceed 0.3 kPa. The complete results of this section of the study are contained in the data of Tables 2 and 3.

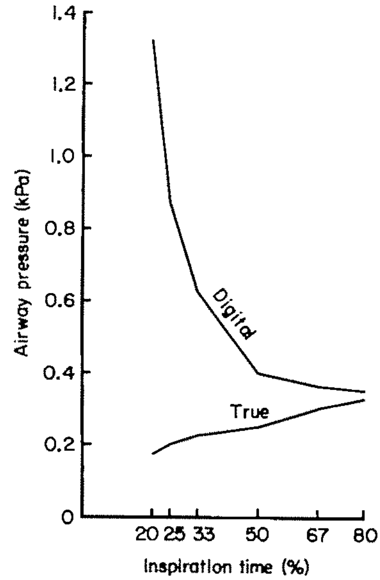

Fig. 1. The effect of increasing inspiratory time from 20 to 80% of the respiratory period on true peak airway pressure and peak airway pressure displayed by the digital meter of the Siemens SV900C ventilator when ventilating a test lung with a tidal volume of 50 ml at a respiratory rate of 40 breaths/minute.

The effects of increasing inspiratory time from 20 to 80% of the respiratory period, with a constant respiratory frequency of 40 breaths/minute, are depicted in Fig. 1. The progressive decline in peak ventilator breathing system pressure conceals the progressive increase in peak intratracheal pressure which occurs throughout the process.

The effects of increasing the cycling frequency from 20 to 120 breaths/minute are depicted in Fig. 2, which reveals that while the ventilator displays a rapid progressive increase in peak pressure (from 0.3 to 6 kPa), the true increase in peak intratracheal pressure throughout this range of ventilatory frequencies is of the order of 0.2–0.3 kPa.

Clinical data

The results of the clinical portion of the study are depicted in Fig. 3. The mean difference between peak ventilator breathing system pressure and peak intratracheal pressure is 0.82 kPa (SD

0.91). The limits of agreement (i.e. the range of values within which 95% of observations would be expected to fall) are from −0.97 to +2.61 kPa. The mean difference between computer calculated peak airway pressure and peak intratracheal pressure is 0.02 kPa (SD 0.10). The limits of agreement are from −0.19 to +0.22 kPa.

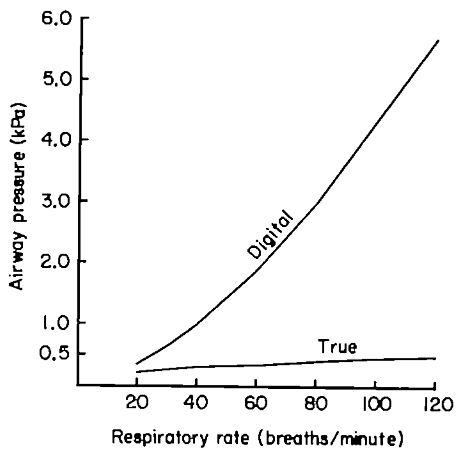

Fig. 2. The effect of increasing respiratory frequency from 20 to 120 breaths/minute on true peak airway pressure and peak airway pressure displayed by the digital meter of the Siemens SV900C ventilator when ventilating a test lung with a tidal volume of 50 ml at a constant I/E ratio of 1/3 (inspiratory time 25%).

Discussion

These studies indicate that peak intratracheal pressure can be calculated from the data of the digital display of the SV900C ventilator. The effects of changes in the respiratory pattern on peak intratracheal pressure can be accurately predicted by incorporating the required calculations into a computer program. The accuracy of the calculations was made possible by three features of the SV900C ventilator: it is equipped with accurate inspiratory flow and expiratory pressure transducers, it has an electrical output suitable for interfacing with a computer, and the paediatric patient system provided with the machine has a minimal compressible volume. The program derived from the data of these studies may appear to be specific to the SV900C but it can be applied to any ventilator which incorporates these design features. It should be noted, however, that the program is specific to a single range of tracheal tubes (Portex) and that it is essential that the tube is used with its matched connector (see Appendix).

The value of this approach is indicated by the findings during the two clinical manoeuvres studied: prolongation of inspiratory time, and increase of respiratory frequency. Prolonged inspiratory times and, indeed, reversed I/E ratios are frequently employed in the management of newborn infants with respiratory distress syn-

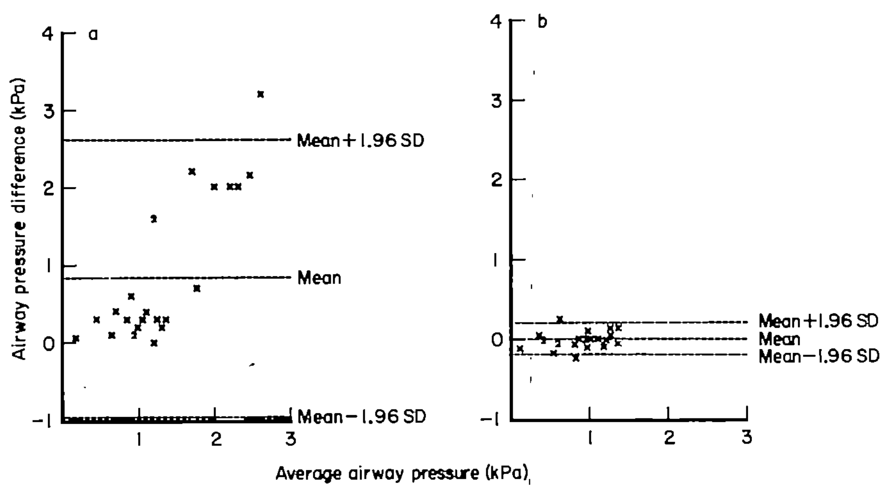

Fig. 3. The mean differences (± 1.96 × SD) between peak ventilator breathing system pressures and directly measured peak intratracheal pressure (a) and computer calculated peak airway pressures and directly measured peak intratracheal pressures (b) in 18 infants and children treated with IPPV.

drome and this approach has been specifically recommended to improve oxygenation without increasing peak airway pressure.[10,11] However, a prospective study[12] has shown a significant positive correlation between long inspiratory times and the incidence of pulmonary barotrauma in neonates who received controlled ventilation of their lungs. A more recent retrospective study[13] produced similar results, although it failed to show a relationship between barotrauma and high peak airway pressures. The explanation of the findings of both of these studies can now be found in the results of bench test d which are depicted in Fig. 1. It is apparent that the decline in peak pressure registered by the ventilator as the inspiration time is increased is quite misleading, and that this process is, in fact, associated with a progressive increase in peak intratracheal pressure. The explanation of this effect becomes apparent if one considers what is happening to flow through the tracheal tube. If the tidal volume and respiratory rate remain constant, the rate of flow of gas through the tube becomes less as the percentage inspiration time increases. Therefore, the pressure gradient along the tube is diminished and the pressure registered by the ventilator decreases.

The converse applies when the high gas flows associated with high cycling frequencies, in the range 60–120 breaths/minute, are employed. The large pressure gradient along the tube in these circumstances is registered as a sharp increase in peak pressure by the ventilator, while the increase in peak intratracheal pressure is minimal. The changes in intratracheal pressure associated with both of these manoeuvres are accurately predicted and described by the computer program.

Appendix

The program runs on a BBC microcomputer. It derives intratracheal pressure by calculating the pressure gradient due to the flow through the tracheal tube and its connector, and subtracting this from the ventilator breathing system pressure measured in the expiratory limb. Since pressures and flows vary continuously throughout inspiration, it is essential to measure both variables frequently during the course of each inspiration so that the shape of the waveforms may be accurately represented, using the technique of linear quantisation. The program thus measures and records both variables approximately 100 times per second. To achieve the required speed, this part of the program is written in 6502 Assembly Language.

The algorithm which calculates pressure gradient due to flow through the tracheal tube was derived from the data acquired in the series of bench tests described under Methods. The program works perfectly for Portex equipment but the errors introduced by substitution of a different type of tube (Mallinckrodt) are minor. This is probably also true in the case of any other PVC tubes. The program also incorporates correction factors for enriched oxygen mixtures. Since the ratio of the viscosity of oxygen to the viscosity of air equals the ratio of the density of oxygen to the density of air, this can be done relatively easily in the case of air/oxygen mixtures without the necessity to determine whether flow is laminar, turbulent or transitional. The program applies a correction factor (CF) to the calculated pressure gradient through the tracheal tube and its connector based on the formula:

$$\mathrm{CF} = 1 + [(\%\ \text{Inspired oxygen} - 21) \times \frac{0.11}{79}]$$

However, the situation is complicated by the fact that the flow transducer of the Servo ventilator is not itself corrected for varying gas mixtures. This was investigated and it was found that the Servo behaved in a manner identical to an uncorrected pneumotachograph. It is necessary, therefore, to apply a correction factor to its flow signal based on the formula:

$$\mathrm{CF} = \frac{1}{1 + [(\%\ \text{Inspired oxygen} - 21) \times \frac{0.11}{79}]}$$

In theory, these correction factors should cancel one another. In practice, they do so almost exactly. Such minor aberrations from exact cancellation as occur are insignificant, and probably result from minor variations between the theoretical and actual properties of gas glow through tracheal tubes. However, since ventilators other than the Servo are unlikely to behave in this fashion, the facility to incorporate correction factors for oxygen enrichment has been retained in the program.

In the case of other gas mixtures such as nitrous oxide–oxygen, the situation would be less simple since the correction factors would vary depending on the nature of the flow at any given time. The program would thus have to calculate Reynold's number and apply different correction factors for laminar, turbulent and transitional flow. These correction factors have been determined for nitrous oxide–oxygen mixtures. However, their incorporation into the program has proven impractical in the case of the BBC microcomputer, due to limitations of memory size and processing speed. They are being incorporated into a new version of the program which is being written to run on a more sophisticated computer. All correction factors described have been validated in bench tests.

During expiration, the program calculates the pressure gradient due to flow through the tracheal tube for each flow value recorded during the previous inspiration, and subtracts this from the appropriate pressure value to calculate intratracheal pressure. The computer then plots the flow, measured ventilator breathing system pressure and calculated intratracheal pressure waveforms on the VDU; and reports peak

and mean inspiratory flows, peak and mean inspiratory ventilator breathing system pressures, and peak and mean inspiratory intratracheal pressures in numerical form. This part of the program is written in BBC Basic.

The data necessary for these calculations are acquired by the computer directly from the Servo 900C via its analogue-to-digital converter. The user is required to enter only the internal diameter and length of the tube in use. The program assumes a linear relationship between tube length and pressure gradient through the tube. No provision is made for any end effects in the program. However, the tubes used in the bench tests which established the magnitude of the pressure gradients, were cut to lengths commonly used in clinical practice. Thus any error due to end effects is likely to be insignificant unless tubes of very unusual length are employed. This was tested in the case of 3.5 mm ID tubes. For this size tube, the pressure gradients were originally determined using a tube 10 cm long. The errors for tubes 5 and 15 cm long were less than 5%. Clearly, end effects are insignificant in this context, relative to the much greater effects of the tube itself and its connector.

The program works for all modes of ventilation available on the Servo 900C ventilator. In an alternative version of the program all data are entered manually by the user. This version is severely limited in that the user must know the flow rate that pertains at the moment of occurrence of peak airway pressure, but has the advantages of being much simpler to implement and being able to predict the likely consequences of proposed changes in ventilator settings on intratracheal pressure.

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The morphine sparing effect of ketorolac tromethamine

A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery

G. W. A. GILLIES, G. N. C. KENNY, R. E. S. BULLINGHAM
AND C. S. McARDLE

Summary

A randomised, double-blind study of patients after upper abdominal surgery was undertaken to assess the analgesic efficacy of ketorolac tromethamine, a new, parenteral non-steroidal anti-inflammatory agent. Postoperatively, patients received a 24-hour intramuscular infusion of either saline ($n = 20$), ketorolac 1.5 mg/hour ($n = 21$) or ketorolac 3.0 mg/hour ($n = 20$). Cumulative morphine requirements were measured using a patient-controlled analgesia system which delivered intravenous increments of morphine on demand. Pain was assessed by visual analogue scores. Arterial blood gas analyses were performed pre-operatively and on the first postoperative day.

Patients who received low and high dose ketorolac infusions required less morphine than the control group ($p < 0.05$ and $p = 0.06$, respectively). This was associated with significantly lower pain scores. Patients who received the higher ketorolac dose had significantly less postoperative increase in arterial carbon dioxide tensions than controls. This study suggests that ketorolac tromethamine is a useful analgesic drug with significant morphine sparing properties.

Key words

Analgesia; postoperative.
Analgesics; non-steroidal.

Intermittent intramuscular injection of opioids remains, despite numerous disadvantages, the most common method of administration of postoperative analgesia.[1] Fear of respiratory depression may lead to analgesia being withheld, which results in irregular administration, fluctuation of plasma levels and inadequate relief of pain. Continuous intravenous infusions of opioids can provide better pain relief[2] but may be associated with respiratory depression.[3] Previous studies have suggested that rectal indomethacin may reduce opioid requirements, improve pain relief and reduce respiratory depression.[4,5] Ketorolac tromethamine is a new, non-steroidal anti-inflammatory agent and is produced in oral and parenteral form. It has significant analgesic properties[6,7] with high potency and exceptional local tolerance. The aim of the present study was to assess the morphine sparing potential of an intramuscular infusion of ketorolac for pain relief after upper abdominal surgery.

G.W.A. Gillies,* MB, FFARCS, Research Fellow, G.N.C. Kenny, MD, FFARCS, Senior Lecturer, Glasgow Royal Infirmary, R.E.S. Bullingham, MB, FFARCS, Medical Adviser, Syntex Research, C.S. McArdle, MD, FRCS, Consultant Surgeon, Glasgow Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER.
* Present address: Senior Registrar, Victoria Infirmary, Glasgow.
Correspondence should be addressed to Dr G.N.C. Kenny please.

Cumulative morphine requirements were assessed with a patient-controlled analgesia (PCA) system developed for this purpose.[8] This permits patients to relieve pain by self-administered increments of an intravenous narcotic and provides a sensitive method for the determination of opioid requirements.[9]

Methods

Consecutive patients scheduled to undergo upper abdominal surgery, who were aged between 18 and 75 years and weighed 45–90 kg, were considered eligible for study. Patients with respiratory, cardiac, hepatic or renal disease, a history of haemorrhagic diathesis, haematemesis, aspirin allergy or risk of pregnancy were excluded. The study was approved by the hospital ethical committee and all patients gave written informed consent.

Premedication was with oral temazepam 20–40 mg; anaesthesia was then induced with a sleep dose of thiopentone and maintained with oxygen, nitrous oxide and enflurane. Muscle relaxation was obtained with vecuronium. Supplementary analgesia was provided by alfentanil as a 1 mg bolus with a maintenance infusion of 0.25–1.0 μg/kg/minute. The infusion was discontinued 20–30 minutes prior to the end of surgery. Two patients with gastric outflow obstruction were considered unsuitable for oral premedication and were given pethidine and promethazine intramuscularly.

Postoperatively, patients were allocated randomly to receive a 24-hour intramuscular infusion of either saline, ketorolac 1% 1.5 mg/hour or ketorolac 1% 3.0 mg/hour drawn from coded ampoules. The infusion was commenced immediately after surgery when the patient was admitted to the recovery area. A loading dose was given by infusion at eight times the maintenance rate for the initial 30-minute period. The effects of ketorolac are principally analgesic rather than anti-inflammatory in the dose range studied. The intramuscular infusions were administered using a Graseby Dynamics battery-powered syringe driver through a 22-gauge Teflon cannula into the deltoid muscle.

In addition, all patients received intravenous morphine on demand for 24 hours. Immediately after surgery the PCA system was attached to the patient's intravenous line via a valved Y-connector. The PCA system comprised an Apple IIe microcomputer linked to an Imed 929 computer-controllable infusion pump.[8] It allowed patients to self-administer increments of intravenous morphine by pressing a hand-held button. The device was programmed to deliver an incremental dose of 0.02 mg/kg of morphine with a minimum interval between doses of 2 minutes. The incremental doses were delivered over approximately one minute to minimise nausea associated with rapid intravenous infusion of morphine. The maximum delivery rate was therefore 20 doses/hour. No more than 0.4 mg/kg could be delivered in any one-hour period and 0.8 mg/kg in any 3-hour period.

Pain was assessed by linear analogue (100-mm) scores at 4–6 hours and 20–24 hours postoperatively. Arterial samples were taken for blood gas analysis pre-operatively and 20–24 hours postoperatively. Nausea was assessed by postoperative requirements for metoclopramide.

Demographic data were analysed using Student's *t*-test and Chi-squared tests where appropriate. The results of morphine consumption, pain scores and changes in arterial carbon dioxide tensions were analysed by a two-tailed Mann–Whitney *U* test.

Results

Sixty-one patients were included in the study. There were no significant differences between groups for age, sex, height, weight or incidence of smoking (Table 1), although the mean dura-

Table 1. Comparison of groups.

	Control (n = 20)	Ketorolac low dose (n = 21)	Ketorolac high dose (n = 20)
Mean (SD) age, years	51 (14)	50 (12)	50 (14)
Female	12	14	11
Mean (SD) height, cm	166 (11)	163 (8)	162 (7)
Mean (SD) weight, kg	59 (7)	63 (12)	63 (12)
Smokers	11	11	10
Mean (SD) duration of operation, minutes	133 (50)	111 (62)	102 (45)*

* $p < 0.05$.

Table 2. Mean (SEM) 24-hour morphine consumption.

	Control (n = 18)	Ketorolac low dose (n = 20)	Ketorolac high dose (n = 19)
Consumption of morphine, mg	78 (9)	53 (7)*	55 (7)

* $p < 0.05$.

Table 3. Mean (SEM) linear analogue pain scores and postoperative increases in $Pa\text{CO}_2$.

	Control	Ketorolac low dose	Ketorolac high dose
4–6 hour pain score	56 (5) (n = 18)	40 (5)* (n = 19)	39 (5)* (n = 18)
20–24 hour pain score	37 (4) (n = 18)	29 (6) (n = 20)	25 (4)* (n = 18)
Increase in $Pa\text{CO}_2$, kPa	0.65 (0.2) (n = 18)	0.13 (0.2) (n = 19)	0.13 (0.1)* (n = 18)

* $p < 0.05$; two patients did not complete pain scores or consent to arterial sampling.

tion of operation in the control group was longer than in the ketorolac groups. Four patients were subsequently withdrawn from the trial and excluded from the analysis of results. One patient from the low dose ketorolac group was withdrawn after 4 hours because of postoperative bleeding; re-exploration revealed an arterial source of haemorrhage. Three patients were withdrawn because of slow respiratory rates. Two women aged 64 developed respiratory rates of 7 and 8 breaths/minute; blood gas analysis revealed $Pa\text{CO}_2$ values of 6.12 and 6.52 kPa, respectively. A 70-year-old man developed a respiratory rate of 4–6 breaths/minute 5 hours postoperatively; his $Pa\text{CO}_2$ was 8.78 kPa. Each of these patients was drowsy but readily aroused. All received supplementary oxygen and none was hypoxaemic. Two were treated with small increments of intravenous naloxone. Two of these three patients were in the control group and one was in the high dose group.

The cumulative 24-hour morphine requirements are shown in Table 2 and Fig. 1. The 24-hour morphine requirements of patients in the control group were greater than for those who received low dose ($p < 0.05$) and high dose ketorolac ($p = 0.06$). Visual analogue pain scores obtained after 4–6 hours were significantly lower in both ketorolac groups compared with controls ($p < 0.05$, Table 3). Pain scores

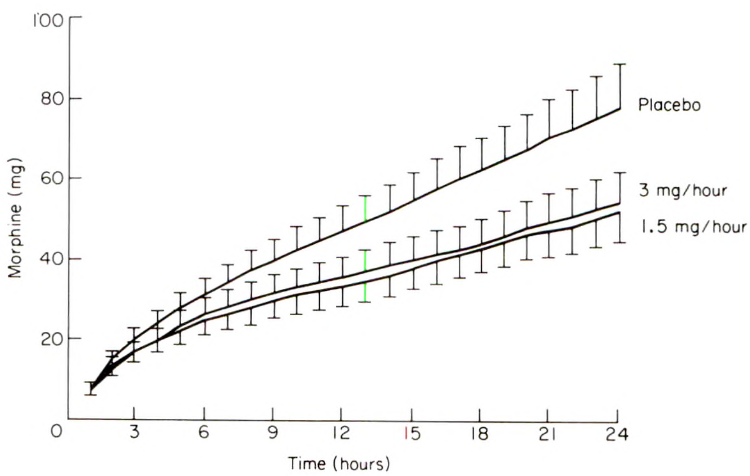

Fig. 1. Mean (SEM) cumulative morphine consumption for control, high dose (3.0 mg/hour) and low dose ketorolac (1.5 mg/hour).

taken at 20–24 hours were significantly lower in the high dose ketorolac group ($p < 0.05$). There was no difference in arterial carbon dioxide tensions between the groups pre-operatively. The mean postoperative increase in arterial carbon dioxide tension was significantly less for those who received high dose ketorolac ($p < 0.05$). There was no significant difference between the groups for postoperative metoclopramide consumption. Two patients complained of a transient, mild discomfort associated with the intramuscular infusion site.

Discussion

This study shows that the intramuscular infusion of ketorolac tromethamine reduces postoperative morphine requirements by almost one-third. This was associated with significantly improved pain scores in patients who received combined therapy. The postoperative increase in arterial $P\text{CO}_2$ was also less in patients who received ketorolac. The observation that the morphine sparing effect was not greater in those who received the higher rate of infusion of ketorolac, suggests that there is a ceiling to its analgesic efficacy. Not only did patients who received a background infusion of ketorolac make fewer demands for morphine, but they also had lower pain scores. This suggests that patients who received morphine alone may have modified their demand for pain relief to avoid unpleasant morphine-related side effects such as clouded consciousness or nausea.

The postoperative increase in arterial $P\text{CO}_2$ was less in those patients who received ketorolac, which suggests that combination therapy may be associated with less opioid-induced respiratory depression. Furthermore, two of the three patients withdrawn from the study because of slow respiratory rates were subsequently found to have received morphine alone. This re-emphasises the desirability of close supervision of respiratory function in patients who receive opioids from a PCA system, especially in older patients who may be unsuitable for this method of analgesia unless continuous respiratory monitoring is available.

Potential disadvantages of non-steroidal anti-inflammatory drugs are the effects on platelet function and the gastrointestinal tract. The only patient who developed unacceptable postoperative blood loss was found to have an arterial source of bleeding. However, we consider that further evaluation of the effects of ketorolac on bleeding time and platelet function is required. We found no evidence of gastrointestinal irritation but we had specifically excluded patients with a recent history of haematemesis who would have been those most at risk.

We conclude from the results of this study that an intramuscular infusion of ketorolac tromethamine has a useful morphine sparing effect in the management of postoperative pain after abdominal surgery. The analgesia produced has a ceiling of efficacy and, if used to supplement morphine for postoperative pain relief, may reduce morphine-related respiratory depression. The use of a parenteral non-narcotic drug such as ketorolac tromethamine would appear to offer worthwhile gains in the immediate postoperative period.

Acknowledgments

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Minimum fresh gas flow requirements of anaesthetic breathing systems during spontaneous ventilation: a graphical approach

K. L. DORRINGTON AND J. R. LEHANE

Summary

A general solution is presented to the problem of finding the minimum fresh gas flow requirements, during spontaneous ventilation, of anaesthetic breathing systems in the Mapleson classification. The solution is applicable to any pattern of breathing, dead space volume and tidal volume. The method is graphical and its use and understanding require no mathematical skills. However, if an analytical form of the respiratory waveform is known, the method is easily extended by use of calculus to obtain a precise analytical solution.

Key words

Equipment; breathing systems, minimum fresh gas flows.

A simple, but precise theoretical method is presented for the determination of the minimum fresh gas flows needed to eliminate rebreathing from anaesthetic breathing systems during spontaneous ventilation. The method is applicable to any ventilatory waveform and provides an immediate visual comparison between all six systems in the extended Mapleson classification A, B, C, D, E[1] and F.[2] The analysis demonstrates inaccuracies in some of the frequently repeated claims made about gas flow requirements.

Theoretical modelling of the rebreathing characteristics of anaesthetic breathing systems is made difficult by the variability of respiratory waveforms and the size of the dead space (V_D) in relation to the tidal volume (V_T). Mapleson[3] adopted a square-wave flow–time ($\dot{V}$–t) waveform and subsequently analysed the F system using a sinusoidal waveform.[2] Experimental studies have confirmed a broad consensus about minimum gas flow requirements, but variability in respiratory waveforms and dead space/tidal volume ratio (V_D/V_T) have contributed to discrepancies.[2,4–7]

Therefore, precise statements about fresh gas flows seem to be justifiable only by mathematical methods incomprehensible to most anaesthetists, and in any case bounded by restrictive assumptions about the shape of the respiratory waveform. However, clinically based conclusions continue to be hotly debated.[8,9] We believe that the following approach provides the clinical anaesthetist with an understanding of this topic from the earliest stage of his training.

The volume against time plot

It has become a convention to represent the pattern of breathing (respiratory waveform) by

K.L. Dorrington, DPhil, DA, Nuffield Research Fellow, J.R. Lehane, MRCP, FFARCS, Consultant, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford.

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plotting gas flow ($\dot{V}$) against time (t).[2,3,10,11] Accurately determined forms of this $\dot{V}$–t waveform for children and adults under halothane anaesthesia have recently been published.[12] The respiratory waveform may just as legitimately be represented by plotting the *volume* (V) of gas passing into and out of the patient against time. Such a plot will take the form shown by the curved line in Fig. 1 (in terms of calculus it represents the integral, with respect to time, of the corresponding $\dot{V}$–t waveform). Time $t = 0$ is taken to be the end of an expiration. In the absence of an end expiratory pause, it is thus the beginning of an inspiration. Volume $V = 0$ is the volume at $t = 0$.

From the origin ($V = 0$, $t = 0$) the volume increases as inspiration proceeds and reaches a maximum V_T at the end of inspiration. The volume then decreases as expiration occurs. Normally the volume of gas expired is closely equal to the volume of gas inspired, and so the plot falls back to touch the horizontal axis at the end of expiration. Small differences between inspired and expired volumes occur due to the respiratory quotient differing from one, to humidification by the lungs of dry gases, and to uptake or elimination of anaesthetic gases. In such cases, the V–t plot will not return exactly to the horizontal axis at the end of expiration.

The fresh gas flow ($\dot{V}_{FG}$) may also be represented on a V–t plot (Fig. 2), by a straight line which has a slope (gradient) equal to $\dot{V}_{FG}$.

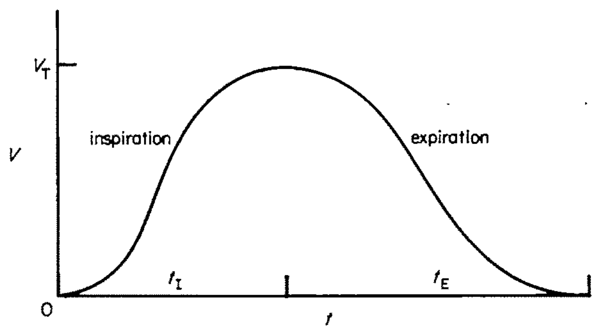

Fig. 1. Respiratory waveform depicted as a plot of volume (V) against time (t). V is the volume of gas that passes into or out of the patient and, since the volume of gas expired is usually closely equal to the volume inspired, the plot returns near to the horizontal axis at the end of the cycle. At both the beginning and end of the cycle the plot would be expected to be horizontal because physiological gas flows ($\dot{V}$) do not change suddenly. V_T is the tidal volume, t_I the duration of inspiration, and t_E the duration of expiration.

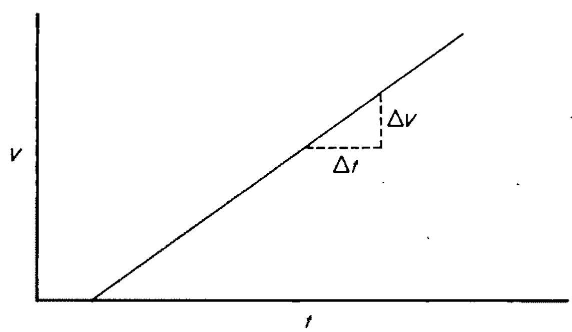

Fig. 2. Fresh gas flow $\dot{V}_{FG}$ depicted as a flow of volume (V) against time (t). The gradient of the straight line ($\Delta V/\Delta t$) equals the fresh gas flow.

The position of this line is varied in the following discussion.

Determination of the minimum fresh gas flows needed to eliminate rebreathing from anaesthetic systems is achieved simply by superimposing the plot of $\dot{V}_{FG}$ (Fig. 2) onto the respiratory waveform (Fig. 1). We adopt the following definitions. *Dead space* (V_D) is the sum of the anatomical dead space and equipment dead space. The equipment dead space is taken to be that volume within the breathing system which lies between the patient's anatomical dead space and the region within the breathing system flushed by the fresh gas flow when the patient is apnoeic. *Rebreathing* is the inhalation into the alveoli of a volume of gas containing carbon dioxide additional to the gas which is present in the dead space at the time inspiration commences.

The Mapleson A (Magill, Lack) system

The fresh gas flow derived is that which, before an inspiration begins, is just sufficient to displace all alveolar gas from the reservoir tube; only the dead space V_D is left filled with alveolar gas. The gradient of line A in Fig. 3 gives the $\dot{V}_{FG}$ which is the solution to this problem.

From the end of expiration ($t = 0$) until point X, where line A becomes a tangent to the respiratory waveform, $\dot{V}_{FG}$ exceeds inspiratory flow and the reservoir bag remains full. The expiratory valve remains open at this early stage of inspiration. From point X the valve is closed and the reservoir bag begins to discharge its contents. The loss of volume of the reservoir bag is given by the vertical distance between the line A and the respiratory waveform. The bag starts to fill when the gradient of the V–t curve becomes less than the fresh gas flow. At Y, where the lines cross, the bag is full and the expiratory valve opens. After point Y, the vertical distance between line A and the waveform is a measure of the volume of expired gas that leaves from the valve. At point Z, a volume $V_T - V_D$ of alveolar gas has left the system and the patient has finished breathing out a volume V_T. The volume of expired gas that remains in the reservoir tube is derived from the dead space and is free of carbon dioxide. Thus rebreathing is eliminated.

Therefore, the gradient of a line which passes through point Z ($t = t_I + t_E$, $V = V_T - V_D$) and is also a tangent to the inspiratory waveform (point X), gives the minimum fresh gas flow requirement for the Mapleson A system.

The Mapleson B and C (Waters) systems

The Mapleson B and C systems have an identical minimum fresh gas flow requirement. This is derived by noting that no alveolar gas must be permitted to enter the reservoir tube (B system) or bag (C system). The gradient of line BC in Fig. 3 gives the $\dot{V}_{FG}$ which is the solution to this problem.

From the end of expiration ($t = 0$) until point X′, where line BC becomes a tangent to the respiratory waveform, $\dot{V}_{FG}$ exceeds inspiratory flow and the reservoir bag remains full. The expiratory valve remains open during this period. From point X′ the valve is closed and

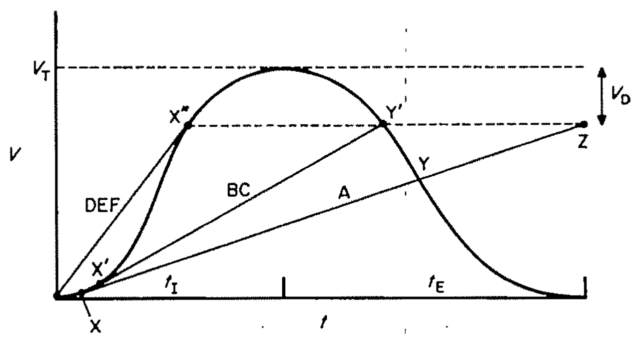

Fig. 3. Respiratory waveform with fresh gas flow lines superimposed to obtain minimal flow requirements for anaesthetic breathing systems (Mapleson A/BC/DEF). V_D is the anatomical and equipment dead space volume.

the bag discharges gas and then fills again until the expiratory valve opens again at Y′. The vertical distance of point Y′ below the peak volume V_T is a measure of the volume of expired gas which has entered the system at the moment the valve opens. In the B and C systems, as long as this does not exceed V_D no alveolar gas will enter the reservoir tube/bag.

Thus the gradient of a line that passes through Y′ ($V = V_T - V_D$ on expiratory limb of waveform) and is also a tangent to the inspiratory waveform (point X′), gives the minimum fresh gas flow requirement for the Mapleson B and C systems.

The Mapleson D, E and F (Bain, T-piece, Jackson–Rees) systems

Finally, the Mapleson D, E and F systems have an identical minimum fresh gas flow requirement. This is derived by noting that from the start of inspiration until a volume $V_T - V_D$ has been inspired, no gas that contains carbon dioxide must be permitted to pass into the equipment dead space from the reservoir tube. The solution is represented by the line DEF in Fig. 3.

From the end of expiration ($t = 0$) until the point X″ where the line $V = V_T - V_D$ crosses the inspiratory limb of the V–t curve, the volume of fresh gas delivered at the T-piece exceeds the patient's inspiratory demand. The excess fresh gas is stored at the patient end of the reservoir tube. At X″ the two volumes become equal and gas which contains carbon dioxide arrives at the T itself. After point X″, gas that contains carbon dioxide may be inspired into the dead space with no functional significance, since it will never reach the alveoli.

Thus the gradient of a line that passes through $V = 0$ at the end of expiration ($t = 0$) and first meets the inspiratory limb of the waveform where $V = V_T - V_D$, gives the minimum fresh gas flow requirement for the Mapleson D, E and F systems.

An important qualification needs to be made for the case in which V_D is so small that a line which joins the origin to the point $V = V_T - V_D$ on the inspiratory limb would cross the limb between these end points. In such a case, elimination of rebreathing requires that line DEF should lie tangential to the inspiratory limb. The appropriate X″ which forms the right-hand end of the line DEF is then the point at which the line becomes a tangent to (parallel to and just touching) the inspiratory waveform. Such a situation is unlikely to arise in clinical practice.

Solutions for the triangular V–t waveform

The simplest conceivable respiratory waveform (Fig. 4) is one in which there is a constant inspiratory flow and a constant expiratory flow. On a flow–time ($\dot{V}$–t) plot this constitutes the square-wave respiratory waveform analysed by Mapleson in 1958.[3] The graphical constructions applied to this waveform are shown in Fig. 4.

Effect of end expiratory pause

We emphasise that line DEF originates at the end of expiration (Fig. 5), which may differ from the beginning of inspiration in the presence of

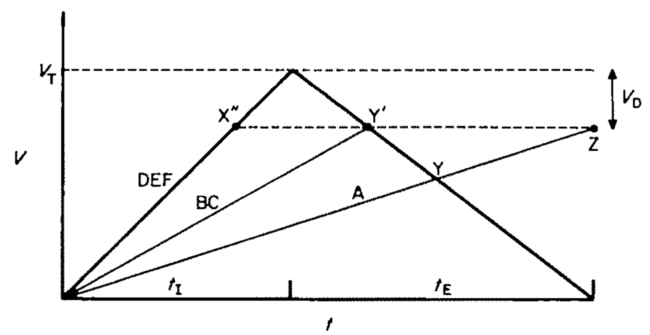

Fig. 4. The equivalent construction to Fig. 3 for the idealised respiratory waveform[3] that consists of constant inspiratory and expiratory flows.

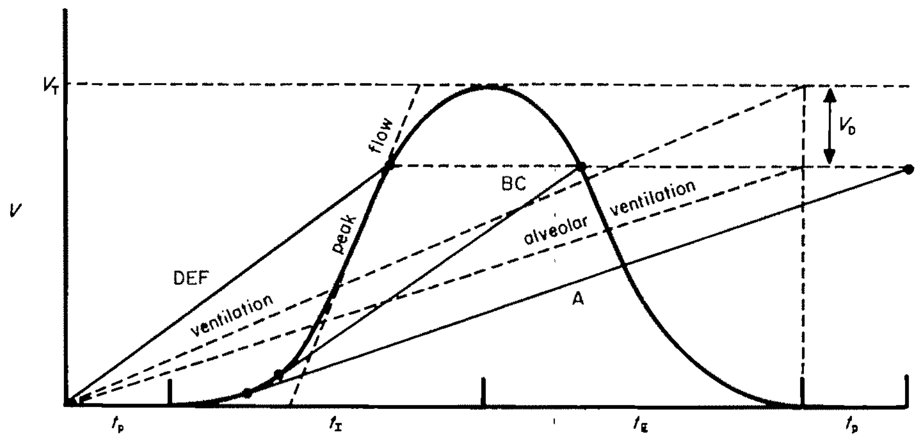

Fig. 5. Construction as in Fig. 3 but with end expiratory pause (duration t_p) preceding inspiration. Also included are three sloping dashed lines the gradients of which equal peak inspiratory flow, ventilation (minute volume) and alveolar ventilation (alveolar minute volume). The completed construction gives a precise comparison between the minimum fresh gas flow requirements of the Mapleson systems A/BC/DEF and the three flows with which comparisons are often quoted in the literature.

an end expiratory pause (t_p). Increasing t_p reduces the slope of line DEF (i.e. reduces the fresh gas flow requirement). However, it can be seen by comparison of the slopes of the fresh gas flow lines, that the Mapleson A system is always more efficient than the other systems. Furthermore, Mapleson B and C systems are more efficient than D, E and F systems except in the presence of a slow respiratory rate (small V_D/V_T) and long t_p, conditions which do not normally prevail during anaesthesia.

Relation to other theoretical conclusions

This analysis makes the usual assumptions of absence of axial mixing within the ducts of the breathing system and that a steady state has been achieved. It demonstrates inaccuracies in some earlier theoretical conclusions that make the same assumptions.

Fresh gas flow requirements are often stated as multiples of either the patient's ventilation (minute volume) or alveolar ventilation (alveolar minute volume). These are given in our construction by the gradients of straight lines that pass through the origin ($t = 0$, $V = 0$) and the respective points $V = V_T$ and $V = V_T - V_D$ at the end of the respiratory cycle ($t = t_p + t_I + t_E$, Fig. 5).

Line A will usually be steeper than the alveolar ventilation line. This shows that it is not accurate to claim that 'theoretically a fresh gas flow equal to the subject's alveolar ventilation should allow at each breath the expulsion of all expired alveolar gas from the system with retention of dead space gas'.[11] The fresh gas flow requirement will usually exceed alveolar ventilation. The difference will be small (Fig. 3) but increases with a slower take-off of inspiration (Fig. 5).

With regard to the B and C systems, it is not accurate to conclude theoretically that 'to completely avoid rebreathing, the fresh gas flow must be equal to peak inspiratory flow'.[13] The peak inspiratory flow is the steepest gradient of the inspiratory limb of the waveform (steepest dashed line in Fig. 5). Clearly, the difference between this gradient and that of line BC will usually be considerable. Even in the extreme case of constant inspiratory flow (Fig. 4), the gradients will be the same only if $V_D = 0$. The B and C systems have been regarded as being highly unstable when operated near their minimum gas flow requirements on account of progressive rebreathing in the event of some expired gas reaching the reservoir tube/bag.[11] However, the current unpopularity of these systems is not the result of dismissal on the basis of careful theoretical and experimental assessment.

Of the three families of breathing systems, the DEF family would appear, from our construction, to have a minimum fresh gas flow requirement which varies most with the shape of the respiratory waveform. It is perhaps for this reason that Dorsch and Dorsch[13] were driven to conclude that there is 'no general agreement'

following a large number of studies to determine this flow requirement. Our findings agree with their broad recommendation of a fresh gas flow approximately equal to 2–3 times the minute volume, but suggest that it is misleading to state dogmatically that 'rebreathing occurs unless the fresh gas flow is at least twice the patient's minute volume'.[14]

Conclusion

We propose our simple but precise graphical construction as a means of understanding and exploring the effect of respiratory waveform, tidal volume and dead space on the fresh gas flow requirements of anaesthetic breathing systems. Immediate visual comparison is provided of the demands of the three groups (A/BC/DEF) in relation to the peak inspiratory flow, ventilation and alveolar ventilation. In the event of unequal expired and inspired volumes (see above), this method of solution remains precise.

It may be thought incorrect to regard a graphical solution as precise. However, a solution may be obtained (within the assumptions given earlier) to a degree of accuracy limited only by the accuracy to which the respiratory waveform, V_D and V_T may be measured and plotted. Moreover, the method is not limited to graphical construction. If an analytical form of the respiratory waveform is known to be appropriate (e.g. sine wave), the graphical solutions are readily converted to precise analytical solutions by use of calculus.

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One year's experience with the APACHE II severity of disease classification system in a general intensive care unit

S. JACOBS, R. W. S. CHANG AND B. LEE

Summary

The APACHE II sickness score was applied prospectively for one year in a general intensive care unit in Saudi Arabia. Two hundred and ten patients were studied, 66 of whom died in hospital. The mean APACHE II score of survivors was 11 (SD 7.1) and of non-survivors, 25.3 (SD 8.8). The mean Risk of Death was 13.3% (SD 13.1) for the survivors and 47.2% (SD 25.8) for non-survivors. The differences in APACHE score and Risk of Death between survivors and non-survivors are highly significant ($p < 0.0005$ for both). No patient survived who had a Risk of Death greater than 60% and none died with a Risk of Death less than 7%. The sensitivity of the APACHE II system in predictions of death can be improved if the scores on the day of admission and on the 3rd day are taken into account.

Key words

Intensive care; APACHE scoring.

The APACHE II system has been shown[1,2] to be a powerful but simple method to determine prognosis in critically ill patients. It has great potential for regular auditing, planning and clinical decision-making, and as a research tool in clinical trials and the assessment of new therapeutic interventions in critical care.

The APACHE II system[1] weights twelve physiological variables (Table 1) according to their degree of deviation from the normal range. Additional scores are given for the age of the patient, the presence of defined chronic disease and whether emergency surgery was performed immediately before admission to the intensive care unit (ICU). The sum of the scores is an expression of the degree of physiological derangement and is independent of the disease process responsible. The Risk of Death is calculated from the APACHE score and coefficients derived from multivariate analysis either of the primary major system affected or of the specific disease. The system has been tested and validated thoroughly in 13 hospitals in the United States.

We chose the APACHE II system in preference to other prognostic and severity of illness scores[3–7] because none of the others has been validated as extensively and because they are without exception more complex and applicable only selectively to certain groups of critically ill patients. We applied this scoring system prospectively for 12 months to all patients admitted to our general intensive care unit to ascertain whether it could be used to determine prognosis in our patient population.

S. Jacobs, FFARCS, Consultant Anaesthetist, Intensive Care Unit, Department of Anaesthesia, R.W.S. Chang, BSc, MS, FRCS, Consultant Surgeon, B. Lee, SRN, Nursing Sister, Nutrition Support Service, Department of Surgery, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia.

Correspondence should be addressed to S. Jacobs please.

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Table 1. The APACHE II severity of disease classification system (from Knaus *et al.*[1]).

Physiological variable	High abnormal range				Normal	Low abnormal range			
	4	3	2	1	0	1	2	3	4
Temperature (rectal) (°C)	⩾41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	⩽29.9
Mean arterial pressure (mmHg)*	⩾160	130–159	110–129		70–109		50–69		⩽49
Heart rate (beats/minute)	⩾180	140–179	110–139		70–109		55–69	40–54	⩽39
Respiratory rate (breaths/minute)	⩾50	35–49		25–34	12–24	10–11	6–9		⩽5
Oxygenation									
If FiO_2 > 50%, (A − a)DO_2 (kPa)†	⩾66.5	46.5–66.4	26.6–46.4		<26.6				
If FiO_2 < 50%, PaO_2 (kPa)					>9.3	8.1–9.3		7.3–8.0	<7.3
Arterial pH	⩾7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Serum sodium (mmol/litre)	⩾180	160–179	155–159	150–154	130–149		120–129	111–119	⩽110
Serum potassium (mmol/litre)	⩾7	6–6.9		5.5–5.9	3.5–5.4	3.0–3.4	2.5–2.9		<2.5
Serum creatinine (mmol/litre)‡	⩾318	180–317	136–179		54–135		<54		
Haematocrit (%)	⩾60		50–59.9	46–49.9	30–45.9		20–29.9		<20
White blood count (× 10^3/cu.mm)	⩾40		20–39.9	15–19.9	3–14.9		1–2.9		<1

Neurological points = 15 − Glasgow Coma Score.

* Mean arterial pressure (mmHg) = (2 × diastolic + systolic)/3.

† (A − a)DO_2 = FiO_2 (101) − $PaCO_2$ − PaO_2.

‡ If acute renal failure has occurred, double score.

Methods

The APACHE score during the first 24 hours of admission to the ICU was calculated for all patients admitted in the 12 months starting on 1 November 1984. The Glasgow Coma Score was the best value over the 24 hours tested whereas all other values were the worst recorded in the same period. Fifty-eight patients remained in the ICU for more than 3 days. The APACHE score of these patients was determined again on the 3rd day.

Continuous ECG and intra-arterial pressure monitoring were used for all patients. Servo 900C ventilators were used for ventilation in patients who required this facility. Core temperature was measured using a rectal probe.

The overall risk of hospital death in this study was calculated from coefficients related to the major organ system insufficiency and from coefficients for specific diagnostic categories, using a multiple logistic regression equation.[1]

The following groups of patients were not included in the study: all myocardial infarction patients admitted to our separate coronary care unit who were not in cardiogenic shock and who did not require ventilation, all postoperative cardiac surgical patients and all children below 12 years of age.

The data were collected by two of us on a special form and entered into an IBM AT microcomputer using a program written in dBASE III, to generate the APACHE II scores, the Risk of Death and to perform statistical analyses. Student's t-test was used to evaluate the significance of differences between groups.

Results

APACHE II score and Risk of Death were determined prospectively in 210 consecutive admissions to the ICU from November 1984 to November 1985. The characteristics of the patients are shown in Table 2. There were 136

Table 2. Characteristics of the 210 ICU patients.

Characteristic		Percentage of total
Male	136	65%
Mean (SD) age, years	43 (19)	
Female	74	35%
Mean (SD) age, years	43 (17.2)	
Major system affected		
Respiratory	78	37%
Cardiovascular	38	18%
Gastrointestinal	33	16%
Neurological	48	23%
Metabolic	8	4%
Haematological	3	1%
Renal	2	1%
Chronic health evaluation		
Positive for chronic health problems	89	42%
Liver	30	14%
Cardiovascular	20	10%
Pulmonary	12	6%
Renal	10	5%
Immune compromised	17	8%
Significant categories		
Nonoperative	100	48%
Postoperative	110	52%
Emergency surgery	48	23%
Operative complications	27	13%
Ward transfers	54	26%
Mean (SD) days on ward before transfer	6 (7)	
Hospital transfers	38	18%
Mean (SD) days in other hospital	5.3 (6.9)	
Mean (SD) stay in ICU, days	5.7 (10.1)	

(65%) male and 74 (35%) female patients with the same mean age of 43 years.

The numbers of patients who underwent operation (110) and those who did not (100), were approximately equal. There were 46 deaths (46%) in the latter group and 20 deaths (18.2%) in the former, of which 15 (75%) occurred following emergency operation.

Table 3 lists the main disease categories associated with death. Approximately two-thirds of the cardiovascular deaths were either due to cardiogenic shock or followed cardiac arrest. Eleven (61%) of the 18 patients in the trauma group with a head injury died; all had a Glasgow Coma Score of less than 5 (i.e. neurological points > 10).

Of the 17 patients with bleeding oesophageal varices, eight were treated medically (including sclerotherapy) and four (50%) of these patients died; nine were managed surgically and, of these, five (56%) died. All nine patients who died were in haemorrhagic shock on admission to the ICU.

Table 3. Main diagnosis or category of the 66 non-survivors.

Diagnosis/category	Total *n*	Non-survivors	
Trauma	37	13	35%
Head injury	(18)	(11)	61%
Non head injury	(19)	(2)	11%
After cardiac arrest	10	7	70%
Cardiogenic shock	8	6	75%
Acute bleeding from oesophageal varices	17	9	53%
Liver failure	9	6	66%
Respiratory failure	28	8	29%
Neurological, excluding head injury	17	7	41%
Other	84	10	12%
Total	210	66	31%

Table 4. Predictive power of APACHE II Risk of Death calculated using specific coefficients and major organ coefficients.

Level of risk		Predicted: To live	Predicted: To die	Predicted: Total	Value of prediction for death: Correct prediction (%)	Predictive value positive (%)	Predictive value negative (%)	Sensitivity (%)	Specificity (%)
Using specific coefficients									
60%	Actual alive	137	7	144	78.6	80.0	78.4	42.4	95.1
	Actual dead	38	28	66					
	Total	175	35	210					
70%	Actual alive	142	2	144	76.7	90.5	75.1	28.8	98.6
	Actual dead	47	19	66					
	Total	189	21	210					
80%	Actual alive	143	1	144	74.7	93.3	73.3	21.2	99.3
	Actual dead	52	14	66					
	Total	195	15	210					
Using major organ coefficients									
60%	Actual alive	144	0	144	79.1	100	76.6	33.3	100
	Actual dead	44	22	66					
	Total	188	22	210					
70%	Actual alive	144	0	144	75.7	100	73.9	22.7	100
	Actual dead	51	15	66					
	Total	195	15	210					
80%	Actual alive	144	0	144	71.4	100	70.6	9.1	100
	Actual dead	60	6	66					
	Total	204	6	210					

Table 5. The APACHE II score and Risk of Death of survivors and non-survivors on day of admission to ICU.

	Survivors	Non-survivors
Number	144 (69%)	66 (31%)
Mean (SD) APACHE score	11.0 (7.1)	25.3 (8.8)
Risk of death derived from major organ system coefficients		
Mean (SD) Risk of Death, %	13.3 (13.1)	47.2 (25.8)
Variance	171.05	664.0
Risk of death derived from specific diagnostic category coefficients		
Mean (SD) Risk of Death, %	14.7 (16.7)	52.8 (26.4)
Variance	278.58	699.22

There is no statistical difference between the different Risks of Death for both the survivors and non-survivors calculated using the two different methods.

Unpaired t-test comparing the APACHE score and Risk of Death of survivors and non-survivors, gave t = 12.05 ($p < 0.0005$) and t = 12.66 ($p < 0.0005$), respectively.

In every case, bleeding was associated with a severe coagulopathy, as a consequence of poor liver function.

Unexpected complications occurred perioperatively in 22 of the 110 who required operation. Seven of these were obstetric patients: severe haemorrhage occurred in six of these, all of whom survived; there was one death from amniotic fluid embolism. Ten of the remaining patients suffered respiratory complications, four of which were related to anaesthesia.

Five miscellaneous problems were also recorded, which included one death related to anaesthesia. Fifty-two patients were admitted electively either following major surgery for stabilisation and monitoring, or because of concern over the possibility of airway problems during the immediate postoperative period.

Forty-three percent of the non-survivors had a specific previous chronic disease. Chronic liver disease was the commonest cause of chronic ill health. Acute renal failure was present in only 4% of the patients. A fifth of the patients were transferred from other hospitals. The mean length of stay in the ICU was 6 days (SD 10.1).

Table 4 shows the predictive power of the APACHE II Risk of Death calculated by using either coefficients for specific disease categories or coefficients for major organ systems. For the same level of risk of death, the specificity is greater using coefficients for major organ systems, although there is some loss of sensitivity.

Table 5 shows the APACHE score and Risk of Death on day 1 of admission to the ICU of the survivors (144) and non-survivors (66), calculated by both methods. Mean Risk of Death, standard deviation and variance for both survivors and non-survivors, calculated by major organ coefficients, are less than the corresponding values calculated by specific coefficients, although the difference in Risk of Death does not reach statistical significance. If major organ coefficients are used, the mean APACHE score of the survivors was 11 (SD 7.1), whilst that of the non-survivors was 25.3 (SD 8.8). The mean Risk of Death of survivors was 13.3% while that of the non-survivors was 47.2%. The differences in the APACHE score and Risk of Death between survivors and non-survivors are highly significant ($p < 0.0005$ for both). Table 6 shows the relationship for all patients between APACHE II score or Risk of Death and the actual number of hospital deaths. In this series there were six non-survivors who had a Risk of Death less than 15%. Brief details of these six patients are given in Table 7. No patient survived who had a Risk of Death equal to or greater than 60%, and none died with a Risk of Death less than 7%.

Table 6. Relationship between APACHE assessments on day 1 and death in hospital. n, total number of patients in each category.

	n	Died	
APACHE II Score			
0–9	67	1	2%
10–19	73	15	21%
20–29	49	31	63%
>29	21	19	90%
Total	210	66	31%
Risk of Death (%)			
0–9	87	4	5%
10–19	39	9	23%
20–49	47	19	40%
50–59	15	12	80%
>59	22	22	100%
Total	210	66	31%

Table 7. Details of the six non-survivors with Risk of Death <15%.

Clinical problem	Age	Risk of Death	APACHE score
Carcinoma of oesophagus, cirrhosis, post oesophagectomy	51	7.4	11
Pneumocystis carinii pneumonia 2 weeks after renal transplant	26	7.5	13
Severe postpartum haemorrhage; transferred 2 weeks later to our hospital in acute renal and respiratory failure (ARDS)	17	9.8	15
Severe head injury, GCS = 4	12	11.1	15
Severe head injury, GCS = 4	33	14.3	17
Polyarteritis with polymyositis, acute renal and respiratory failure on admission	40	14.4	18

ARDS, Adult respiratory distress syndrome; GCS, Glasgow Coma Score.

Table 8. Predicted and actual outcome for 58 ICU patients with APACHE scores on day of admission and day 3 in ICU.

	Predicted		
	To live	To die	Total
*Patients predicted to die with Risk of Death of 60% or more on day 1**			
Actual			
Alive	34	0	34
Dead	19	5	24
Total	53	5	58
Patients predicted to die with Risk of Death of 60% or more on day 1 or *Risk of Death less than 60% on day 1 and deterioration on day 3 so that the Risk of Death was 30% or more†*			
Actual			
Alive	34	0	34
Dead	17	7	24
Total	51	7	58

* Sensitivity 20.8%; specificity 100%. Correct 67.2%; predictive value positive, 100%; predictive value negative, 64.2%.

† Sensitivity 29.2%; specificity 100%. Correct 70.7%; predictive value positive, 100%; predictive value negative, 29.2%.

Table 8 shows the predictive power of the APACHE II system for the 58 patients who remained in the ICU for more than 3 days. At a Risk of Death level of 60% or more on day 1, all five patients predicted to die, died. This gives a specificity of 100% and a sensitivity of 21%. When *two* Risk of Death values (days 1 and 3) are taken into account, the sensitivity of prediction is increased to 29%. This is achieved by redefining the criteria which predict death. Patients predicted to die are those who had *either* a Risk of Death of 60% or more on day 1 *or* a Risk of Death less than 60% on day 1 but had deteriorated by day 3 so that their Risk of Death was equal to or greater than 30%.

Discussion

This study of 210 ICU patients shows that the APACHE II severity of disease classification system gave results comparable to those obtained by Knaus *et al.*[1] in the United States and Ledingham's group[2] in the United Kingdom, and confirms the reliability of this system in different populations. We found that the specificity of the APACHE II system for prediction of death among our patients increased when the coefficients derived for major organ systems were used instead of those for specific diagnostic categories. One possible reason for this is that our patient population differs from that in the United States where the system was developed, and matches more closely the *pot pourri* of American patients categorised under the major organ systems.

We have shown that the sensitivity of the APACHE II system can be improved by using criteria based on two APACHE scores to reflect the dynamic pathophysiological states of ICU patients. The original APACHE system was not developed to be used for individual patient treatment decisions but we believe that the specificity and improved sensitivity of prognostic prediction obtained by performing *two* determinations of APACHE score and Risk of Death, can form a foundation for the development of criteria on which to base clinical decision-making. We have tested this premise successfully on patients who required total parenteral nutrition in the ICU.[8,9] However, each ICU should test the APACHE system in order to determine the criteria required to predict death in its own patient population.

In the future, we shall use the APACHE II classification system, *in conjunction with clinical considerations*, to determine priorities for

admission to, and discharge from, our ICU. Thus, in the common situation in which several patients are referred for admission to a limited number of beds, patients who have a Risk of Death less than 7% or greater than 60% may be discharged to make room for other patients more likely to benefit from intensive care.

We shall also estimate the APACHE II score and Risk of Death daily, together with the final score when the patient either dies or is considered clinically fit to leave the ICU. These data will enable an evaluation of trends in physiological derangements and of the patient's response to treatment.

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CASE REPORT

Unstable cervical fracture

Anaesthetic management for an urgent Caesarean section

J. R. EASON, C. N. SWAINE, P. I. E. JONES, M. J. GRONOW AND A. BEAUMONT

Summary

The anaesthetic management of a 26-year-old woman who sustained an unstable fracture of C_2 when 40 weeks pregnant, is described.

Key words

Anaesthesia; obstetric.
Complications; fracture, cervical spine.

Reports of trauma in pregnancy are not uncommon. We report such a patient who had an unstable cervical fracture and required urgent Caesarean section.

Case history

A 26-year-old, 75 kg, sickle-cell negative West Indian woman was involved in a road traffic accident on the day she was due to deliver her second child. As a result of a whiplash injury she sustained a fracture of the cervical spine. On arrival in the accident and emergency department she had severe spasm of her neck musculature and was in considerable distress. She had not lost consciousness and had no neurological signs indicative of spinal cord compression. There were no other injuries.

Radiographs of her cervical spine revealed a fracture of both pedicles of the second cervical vertebra (C_2) with anterior subluxation of the body of C_2 upon C_3 (Fig. 1). This was, therefore, an unstable fracture. Immediately after the accident she went into early labour and was experiencing four uterine contractions every 10 minutes. Examination revealed that the fetus was alive, the head was engaged, the cervix was 1 cm dilated and uneffaced and the membranes were intact.

Crutchfield tongs were affixed to the patient's skull under local anaesthesia and 4.5 kg traction was applied to her neck. Prior to this she had received two injections of pethidine 75 mg and one injection of prochlorperazine 12.5 mg, following which her uterine contractions had settled.

After discussion between the orthopaedic, obstetric and anaesthetic staff involved in her management, it was decided that the hazards of a vaginal delivery in the presence of an unstable cervical fracture were too great and that she should undergo urgent Caesarean section. Epidural anaesthesia was felt to be contraindicated, since the fracture was considered to be unstable in flexion and any attempt by the patient to adopt a lateral position, or flex her spine, would jeopardise her cervical cord. Accordingly it was decided that a Caesarean section should be performed under general anaesthesia.

The proposed course of action was discussed

J.R. Eason, FFARCS, MRCP, Senior Registrar, C.N. Swaine, FFARCS, Registrar, P.I.E. Jones, FFARCS, Consultant, M.J. Gronow, MD, MRCOG, FRACOG, Lecturer, A. Beaumont, FRCS, Orthopaedic Registrar, King's College Hospital, Denmark Hill, London SE5 9RS.

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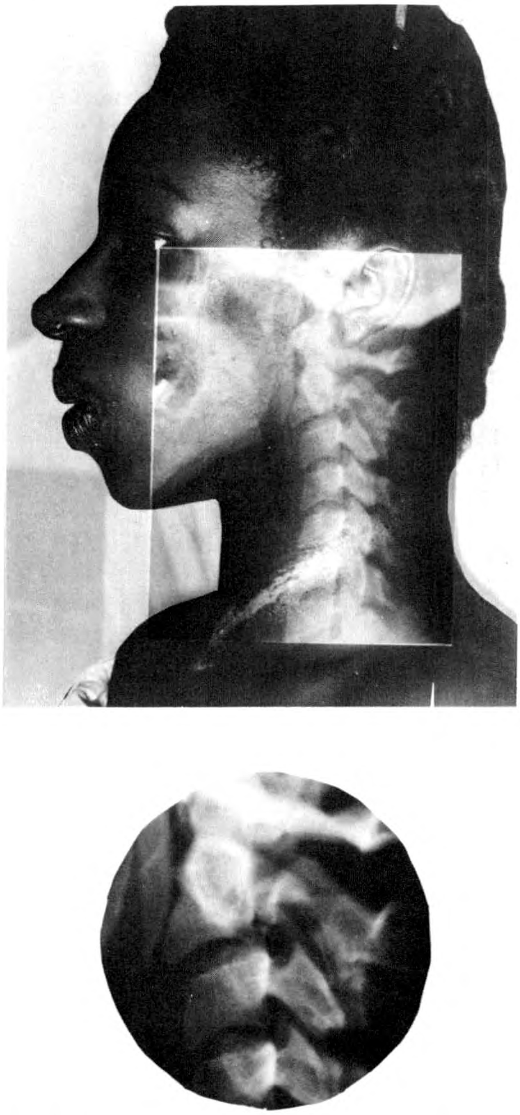

Fig. 1. This shows the position in which the patient was intubated. Both laminae of C_2 are disrupted and the body of C_2 is subluxed anteriorly on that of C_3. The space between the spinous processes of C_1 and C_2 is widened.

with the patient, who was in a somewhat emotional state owing to her discomfort and entirely reasonable anxiety about the possibility of paralysis. She had received her last dose of intramuscular pethidine at 11:45 hours and it was decided that no more should be given in view of its known tendency to delay gastric emptying. She was given ranitidine 150 mg orally at 13:45 hours, 15 ml oral mist magnesium trisilicate at 14:00, 15:00 and 16:00 hours and 10 mg intramuscular metoclopramide at 15:00 hours.

At 16:00 hours the patient was transferred to the operating theatre where ECG and arterial blood pressure monitoring were instituted. All available aids to intubation were assembled. Cervical traction was maintained while the patient was transported to the operating theatre and, prior to induction, her neck was further splinted by means of a VAK-PAK (Howmedica Ltd, Rutherford, NJ, USA). This is a flexible plastic bag filled with polystyrene balls, which takes on whatever shape it has at the time when the air inside it is evacuated by suction. The VAK-PAK was slipped beneath the patient's neck and wrapped around her neck and jaw so that it was closely applied to their contours. On evacuation it rigidly conformed to the neck and thereby prevented undesirable neck movement.

The patient's lungs were pre-oxygenated for 5 minutes. An inhalational induction using halothane in 100% oxygen was commenced and cricoid pressure was applied. The patient became mildly agitated after about 2 minutes when breathing 2.5% halothane, at which point thiopentone 150 mg was given intravenously. An oral airway was inserted and the patient was settled breathing 3% halothane in 100% oxygen. Gentle manual compression of the reservoir bag demonstrated that it was possible to inflate the patient's lungs without moving her head. Once this had been established, suxamethonium 100 mg was given intravenously and direct laryngoscopy was performed using a Macintosh blade. As anticipated, intubation proved to be difficult since it was not possible to visualise the larynx without extending the patient's neck. This constituted an intubation of grade III difficulty according to the classification of Cormack and Lehane,[1] in which only the epiglottis could be seen. The glottis was located by gentle anterior probing with a flexible introducer protruding 5 cm from the tip of a cuffed 8.0-mm Magill tracheal tube. The trachea was then intubated although momentary difficulty was experienced when the tube snagged at the level of the cords. Vecuronium 6 mg was then given intravenously and the lungs mechanically ventilated with 50% nitrous oxide to which 0.5% enflurane was added.

A normal male infant was delivered by lower segment Caesarean section. Since his Apgar score at birth was 1, his trachea was intubated

for a total of 3 minutes. Apgar scores at 5 and 10 minutes were 8 and 10, respectively.

Immediately after delivery 5 units of Syntocinon and 10 mg papaveretum were given intravenously and the nitrous oxide concentration was increased to 66%. Droperidol 2.5 mg was given intravenously, both for its antiemetic effect and to minimise restlessness at the time of extubation. A wide-bore nasogastric tube was passed and 300 ml of clear fluid aspirated. Neuromuscular blockade was reversed without difficulty at the end of surgery and tracheal extubation was performed with the patient supine, head down and still in traction.

A neurological examination carried out after recovery from the anaesthetic revealed no evidence of spinal cord damage. The patient remained on skull traction for 6 weeks and subsequently made a good recovery from her injury.

Discussion

Induction of anaesthesia and intubation of this patient carried the risks of tetraplegia and respiratory paralysis had further subluxation occurred at the fracture site during intubation, aspiration of gastric contents during attempted intubation, and fetal depression and increased uterine bleeding due to the use of high concentrations of halothane. Standard obstetric anaesthetic practice aims to minimise the risk of aspiration by means of a rapid sequence induction with full muscle relaxation, whereas induction of a patient with an unstable cervical fracture is best achieved by techniques which minimise neck movement[2] and are of necessity time consuming.[3–8] Ideally, spontaneous respiration should be preserved and in all cases a clear airway is essential lest attempts at intubation fail.[9] We chose our anaesthetic method after careful consideration of the circumstances of the case and of the techniques available to us.

The patient had a normal delivery 8 years previously, which was followed by a postpartum haemorrhage. The possibility of permitting normal labour was considered. However, the risk of involuntary neck movements, particularly during the second stage, and the dangers of emergency anaesthesia in the face of obstetric complications, were deemed unacceptable.

A Caesarean section under epidural or spinal blockade was ruled out by the orthopaedic surgeons, who were strongly of the opinion that both spinal flexion and the adoption of a lateral or sitting position would have been very hazardous in this patient. The possibility of holding the patient rigid in a rotating Stryker frame was considered but the chances of success in an anxious, somewhat obese, unflexed patient were thought to be slight. Additionally, the patient herself was strongly in favour of general anaesthesia and we felt there was a possibility that she might panic during surgery under regional anaesthesia.

Caesarean section can be performed with local anaesthetic infiltration of the skin and underlying structures. This often requires up to 100 ml of lignocaine or prilocaine 0.5%, which may be associated with manifestations of systemic toxicity. Convulsions that required emergency intubation in this patient might have been disastrous. Moir[10] considers this technique 'far from satisfactory', an opinion shared by one of the authors (J.E.) who has witnessed it whilst practising abroad. In this case, lack of familiarity with the technique, combined with a marked reluctance on the part of the patient to undergo any form of local anaesthesia, decided us against this approach.

The choice, therefore, lay between awake intubation followed by general anaesthesia, intubation with or without the help of a neuromuscular blocking agent after induction of general anaesthesia, or induction and maintenance of general anaesthesia without intubation, using an inhalational agent and spontaneous ventilation. It was anticipated that intubation might not be straightforward and the advantages of an awake intubation would have been the maintenance of protective muscle spasm around the fracture site and the preservation of upper airway reflexes. This technique is favoured by most North American authors. However, most 'awake' intubations require substantial doses of sedatives[3,5–7,11–16] and, once the larynx has been adequately anaesthetised, aspiration becomes a serious risk. This patient had vomited on her way to the operating theatre and it had proved difficult to restrain her natural inclination to rotate her neck in order to expel material from her mouth.

Fibreoptic bronchoscopy by the nasal route is more difficult in a supine patient, even if the tongue is pulled anteriorly, and coughing, gagging and vomiting were all highly undesir-

able. Muscle spasm, although important, does not entirely protect the spinal cord from the consequences of uncontrollable movements. Appropriate equipment and expertise were available but we decided against awake intubation in this case for all the above reasons, but principally because we felt the patient would have difficulty cooperating with the procedure.

Intubation without relaxants following induction of anaesthesia with an inhalational agent or ketamine was considered but rejected because of the expected anatomical difficulties. Alternatively, intubation could have been attempted after a standard rapid sequence thiopentone–suxamethonium induction but failure to intubate might have led to an unacceptable degree of neck movement and carried the risk of total loss of the airway. The use of suxamethonium is contraindicated more than 24 hours after actual cord trauma but this patient had no evidence of this and her injury was less than 24 hours old.[17] Suxamethonium is also considered dangerous if there are bone fragments held in place solely by muscle spasm; this point was discussed with the orthopaedic staff and it was felt that cord damage was unlikely in this case even if relaxants were used, provided that no external movement was permitted.

Had it proved impossible to intubate this patient without an unacceptable degree of neck movement, it was our intention to continue the anaesthetic using an inhalational agent and spontaneous ventilation. In the event, the patient underwent a modified inhalational induction and it proved possible to ventilate her lungs manually. Visual intubation was achieved, albeit with difficulty, after the use of suxamethonium. The tendency of a Magill tube to 'snag' at the level of the cords during a guided intubation has been commented on by other authors.[1] In retrospect, we feel that an Oxford tube, with its 90° angle and posteriorly facing bevel, might have been a more suitable choice. Manual ventilation was hazardous, insofar as inadvertent inflation of the stomach might have precipitated vomiting. We felt, however, that the risk of failing to intubate and finding that we could not ventilate the patient, would have forced us to move her neck and we considered that the avoidance of spinal cord trauma at the C_2 level took precedence over the ever-present risk of aspiration of gastric contents.

This was a difficult case and we consider that there is no entirely correct method of management. Awake intubation has its advantages and would have been the safest technique but it is not acceptable to all patients in this country and we suspect that few anaesthetists are so skilled in its use that they would unhesitatingly employ it in a case such as this.

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Anaesthesia, 1987, Volume 42, pages 750–753

CASE REPORT

Gross hypernatraemia associated with the use of antiseptic surgical packs

J. M. THORP, I. MACKENZIE AND E. SIMPSON

Summary

A severely ill patient with gas gangrene developed hypernatraemia associated with the use of wound packs soaked in a hypertonic solution called Eusol substitute, a commonly used stable alternative to true Eusol.

Key words

Ions; sodium.
Sterilisation; wounds.

Eusol (Edinburgh University Solution of Lime) is an unstable solution of calcium hypochlorite with a variable content of available chlorine, and must be prepared immediately before use. A common alternative solution (in all the main Scottish hospitals) is diluted Milton (a stabilised, buffered sodium hypochlorite solution in hypertonic saline), which has a higher available chlorine content. The substitute is at least as effective as an antiseptic but is very different in terms of chemical composition, osmotic effect and pH (Table 1). Clinical and biochemical sequelae might be expected from these differences but, to our knowledge, have not been reported previously.

Case history

A 53-year-old man was admitted to the surgical intensive care unit (SITU) with septicaemia associated with gas gangrene of the right thigh and buttock, which originated from an ischiorectal abscess. During the first week he remained extremely ill, required artificial ventilation of the lungs and received an appropriate antibiotic regimen. His wounds were irrigated with hydrogen peroxide and dressed twice daily with packs soaked in Eusol substitute: approximately 0.5 litre of solution was used each time the packs were changed. Bleeding from raw surfaces was replaced with concentrated red cells and plasma

Table 1. A comparison of sodium concentration, chloride concentration, osmolality and pH of standard Eusol and Eusol substitute.

	Standard Eusol	Eusol substitute	Reference values (plasma)
Sodium (mmol/litre)	0	780	133–145
Chloride (mmol/litre)	113	730	95–105
Osmolality (mosmol/kg)	245	1590	275–295 (male)
pH	8.4	11.0	7.36–7.44

J.M. Thorp, MRCP, FFARCS, Consultant, I. Mackenzie, FRCS, Consultant Surgeon, E. Simpson, MCB, MRSC, Principal Biochemist, Monklands District General Hospital, Airdrie ML6 OJS, Lanarkshire, Scotland.

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Table 2. A record of fluid balance and blood product transfusion during the patient's hypernatraemic phase.

Day in SITU	Fluid (ml)	Measurable fluid loss (ml)	Fluid balance (ml)	Cumulative fluid balance (ml)	PCV	Blood products given in addition to fluids* (ml)
1	4610	3135	+1475		0.37	2200
2	4102	4380	−278	1197	0.26	1600
3	3657	3735	−78	1119	0.27	1600
4	2843	3385	−542	577	0.29	1000
5	4242	2790	+1452	2029	0.36	
6	2817	3020	−203	1826	0.35	800
7	3445	2465	+980	2806	0.33	
8	4410	3035	+1375	4181	0.30	400
9	3730	2980	+750	4931	0.33	400
10	3895	3040	+855	5786	0.35	600
11	4009	2821	+1188	6974	0.29	
12†	6570	3585	+2985	9959	0.30	400
13	6787	4277	+2510	12 469	0.36	200
14	3382	4325	−943	11 526	0.30	400

* 19 units of concentrated red cells and about 6 litres of other blood products.
† Plasma sodium 168 mmol/litre.

(Table 2). Deterioration in pulmonary function during the first week resulted in no immediate possibility of weaning from the ventilator, and total parenteral nutrition (TPN) was started with 1 litre Synthamin 9 and 1 litre 50% dextrose per day, with appropriate insulin therapy and vitamin and mineral supplements. His plasma sodium concentration increased during this period (Fig 1).

During the second week, the frequency of wound dressing was increased from twice to three times a day and the plasma sodium concentration continued to increase. Fluid input and losses were monitored carefully and the volumes of 5% dextrose added to the daily intravenous fluid regimen to maintain water balance were varied accordingly. Aminoplex 12 was substituted for Synthamin in an effort to reduce

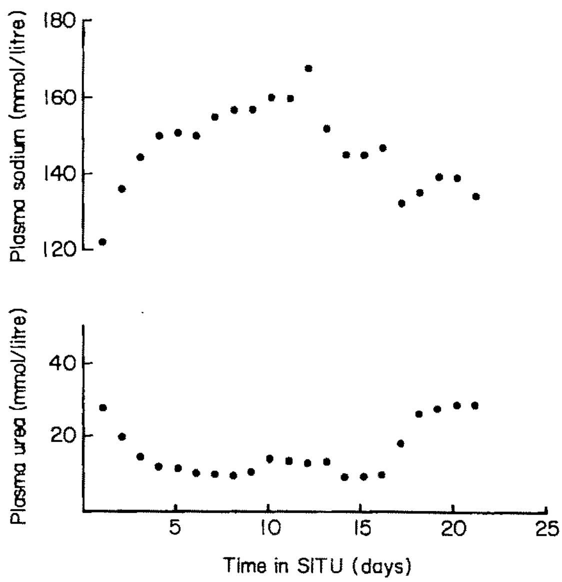

Fig. 1. Plasma sodium and urea values while the patient was in the SITU.

sodium input; this resulted in an average daily parenteral sodium input of 72 mmol/day including drugs. Despite these measures, the plasma sodium concentration on day 12 increased to 168 mmol/litre and the patient's general condition deteriorated further. TPN was discontinued for 12 hours and 5.5 litres of 5% dextrose were given over a 24-hour period. The hourly urine output halved while the TPN was discontinued. The plasma sodium concentration had decreased to 152 mmol/litre by the next day. Additional 5% dextrose was given over the next day and the plasma sodium concentration decreased to within normal limits. No oedema was apparent at any stage. A sample of Eusol substitute was analysed in the laboratory (Table 1) and, consequently, his wounds were dressed thereafter with packs soaked in an isotonic antiseptic solution. During the third week in SITU, multiple organ failure supervened and the patient died 21 days after admission.

Discussion

Theoretically, gross hypernatraemia could be due either to water depletion or to an excess of sodium.[1] With regard to water depletion, the fluid balance was positive on each day during the second week and the cumulative fluid balance was positive while the plasma sodium concentration was high and increasing (Table 2). There was no other discernible site of water loss. Significant osmotic water movement does not occur across an intact skin barrier[2] but the use of topical dressings when the skin is either damaged, as in burns, or bypassed, as in this case, may result in the establishment of an osmotic gradient.[3,4] In this case, a large, raw wound area was in contact with packs soaked in a hypertonic solution and water loss into the packs could be expected to occur. Paradoxically, urine output was maintained at around 3 litres/day during the hypernatraemic phase (Table 2). Oliguria

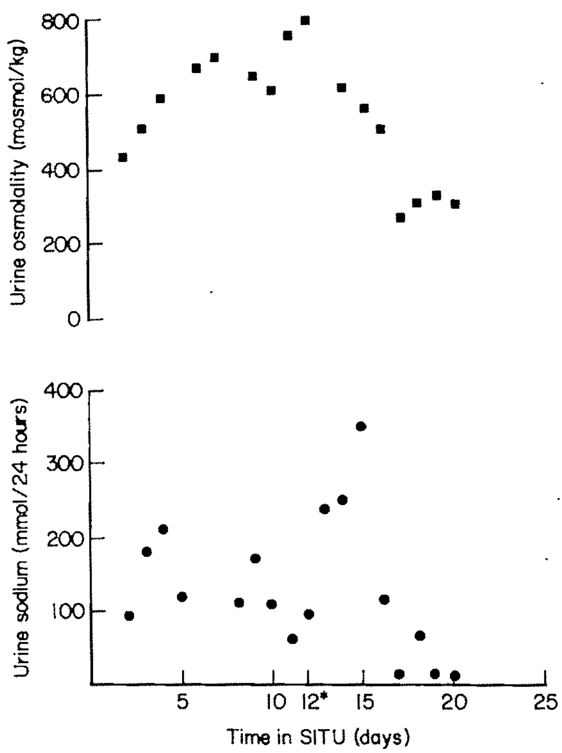

Fig. 2. Urine sodium and osmolality values while the patient was in the SITU. Normal sodium output 50–200 mmol/24 hours. *Plasma sodium 168 mmol/litre on day 12.

is normally a good indicator of dehydration because of the sensitivity of the osmoreceptors associated with antidiuretic hormone (ADH) production.[5] However, a large osmotic load can cause over-riding of the ADH effect.[6] This patient's urine was hyperosmolar (Fig. 2). Urine volumes decreased in the 12 hours during which TPN was discontinued and it was realised that TPN had resulted in additional obligatory water loss.

Alternatively, hypernatraemia could have been due to an excess of sodium. This is a less common cause than water depletion because sodium is predominantly an extracellular ion: small increases in sodium cause water movement into the circulation, which minimises changes in sodium concentration, and renal excretion of the excess sodium occurs. However, infusion of hypertonic saline[7] or external saline,[8] particularly if associated either with an inability to drink or with poor renal function, may cause hypernatraemia. High body sodium is usually associated with oedema. In this case there was no enteral input, parenteral sodium administration was within normal limits and oedema was absent. However, in addition to a high sodium content, Eusol substitute also has a high chloride content (Table 2). As the plasma chloride concentration was also high (reaching 132 mmol/litre on day 12), it seems likely that some absorption of sodium chloride from the packs did occur; lack of oedema was due possibly to concurrent water loss. It has been shown previously that the absorption of various substances may occur when the skin barrier is breached[4,9,10] and loss of sodium from burned and other de-epithelialised surfaces into topical cream has been demonstrated.[11] It was concluded that the hypernatraemia was the result of sodium absorption compounded by simultaneous water loss by osmosis into the packs. In addition, protective mechanisms against hypertonicity were lacking due to the patient's inability to complain of thirst or to drink, and a reduction in renal conservation of water.

This case highlights one of the hazards of verbal prescription. It is common for wound dressings to be ordered verbally and Eusol packs requested in this way may result in the application of Eusol substitute. The clinical problem described would not be expected to occur with true Eusol or with small quantities of the substitute. It would seem reasonable when topical applications are used in large volumes on raw surfaces, to ensure that they are nearly isotonic, as well as that they have the desired therapeutic effect. Solutions that contain unnatural substances require particular vigilance and solutions of natural ions should approximate to physiological concentrations.

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Anaesthesia, 1987, Volume 42, pages 754–756

CASE REPORT

Spinal anaesthesia following facet joint injection

A report of two cases

J. C. GOLDSTONE AND J. H. PENNANT

Summary

Case histories of two patients who developed spinal anaesthesia following facet joint injections are described and the possible mechanisms discussed.

Key words

Anaesthetic techniques, regional; facet joint blockade.
Complications; hypotension.

Lumbar facet joint blockade using local anaesthetics is a common procedure for the diagnosis and relief of chronic low back pain.[1] Facetal rhizotomy using radiofrequency thermocoagulation is a related technique that may also be rewarding.[2]

The patient is placed prone with a pillow beneath the abdomen to flatten the lumbar lordosis, using X ray screening facilities and intravenous sedation. A 20- or 22-gauge spinal needle is inserted percutaneously above, or slightly lateral to, the diseased joint and guided through the joint capsule. This is often felt as a loss of resistance, but is confirmed by injection of 0.25 ml contrast medium. The joint should be clearly outlined and 2–3 ml 0.5% bupivacaine and 20 mg Depo-Medrone are used to block the joint. The joints above and below should also be injected, because of sensory overlap with adjacent dermatomes. If successful, pain relief is usually immediate and some patients are discharged the same day.

We report here two patients who developed unexpected complications following the procedure.

Case histories

Case 1

A fit, 42-year-old man with a 7-year history of low back pain was admitted for facet joint injection. He was placed prone. A 20-gauge spinal needle was inserted into each of the three lower left lumbar facet joints. Correct positioning was confirmed using X ray screening and contrast medium. From a 20-ml syringe, 2 ml 0.5% bupivacaine was injected into each joint. He complained of a feeling of warmth and of paraesthesiae in the buttocks immediately following the third injection. He felt faint. Over the next 10 minutes he demonstrated an ascending sensory loss which reached the level of C_6. He complained of nasal stuffiness and had a bilateral ptosis and miosis. The pulse rate decreased to 30 beats/minute and arterial pressure to 70/30 mmHg. This responded promptly to atropine 0.6 mg and 2 litres of crystalloid fluid intravenously. He experienced difficulty in breathing on admission to the intensive care unit although a respiratory rate of 15 breaths/minute

J.C. Goldstone, MB, BS, Registrar, J.H. Pennant, MB, BS, FFARCS, Senior Registrar, Department of Anaesthesia, King's College Hospital, Denmark Hill, London SE5 8RX.

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achieved normal arterial blood gases. No active intervention was needed. The blockade receded over the next 8 hours and he made an uneventful recovery.

Case 2

A 37-year-old man presented with a 5-year history of low back pain. The first lower right facetal joint was identified utilising X ray screening with contrast. The patient reported a rapid onset of paraesthesiae immediately following injection. This ascended to the level of T_3 at 5 minutes. This patient experienced no cardiorespiratory embarrassment. He was admitted to the intensive care unit for observation and made an uneventful recovery.

Discussion

Earlier studies of facet joint blockade did not record any significant complications.[3,4] Indeed, many authors have emphasised the simplicity and safety of the procedure.[1,5] The mechanisms by which a high spinal and total spinal anaesthesia ensued in our patients are unclear but four possible explanations exist.

Firstly, the needle may have been inserted through or beside the facet joint, into the intervertebral foramen, to penetrate the dura; this would result in a massive subdural or subarachnoid injection. Secondly, the needle could have entered the epidural space, again by traversal of an intervertebral foramen. Thirdly, subarachnoid injection may have resulted from penetration of the needle into a dural cuff that protruded through the intervertebral foramen. Finally, local anaesthetic may have been injected into the lumbar nerve itself.

Direct injection into the subdural or subarachnoid space could have occurred, and is more likely with the lateral approach used in our cases. It is difficult to penetrate the intervertebral foramen if the skin entry point is directly above the joint. Injection into the epidural space is unlikely to occur at three separate levels and, with the volumes of local anaesthetic used, it would be unusual to produce high or total spinal anaesthesia.

However, epidural spread can occur following a correctly placed facet joint injection; Dory[3,6] commented on the large size of the capsular recesses of the facet joints, particularly on their medial side adjacent to the intervertebral foramen, and on the frequency with which the capsules ruptured during or after arthrography. The volume of the joint is approximately 2–3 ml, so it is easy to see why capsular rupture is so common when these volumes of contrast media and local anaesthetic are used. Using computerised tomography he demonstrated leak of contrast medium into the epidural space after capsular rupture. Again, it would be unusual to achieve such a high spinal anaesthesia through this mechanism. Dural cuffs may extend past the intervertebral foramen. It is possible to inject into the dural cuff with the inevitable consequence of spinal anaesthesia.

Endoneural injection is also known to result in extensive spread of local anaesthetic.[4,7] Perineural spaces have been demonstrated to transmit dye and local anaesthetic agents directly into the subarachnoid space, both in animals and in man; this results in high spinal anaesthesia.[8,9] The sequelae in our patients could be explained in this way even if this complication had occurred during only one of the three injections.

Whatever mechanism was responsible, high or total spinal anaesthesia can ensue from facet joint blockade using local anaesthetic solutions. This procedure is widely practised, often without screening procedures, on patients admitted as day cases. Resuscitation facilities are often absent. As is the case for all local anaesthetic blocks, a full range of resuscitation equipment including intravenous infusions, resuscitation drugs, oxygen, facemasks and equipment for tracheal intubation, ECG and defibrillator facilities and a person skilled in their use, must be readily available so that this complication can be quickly diagnosed and promptly treated.

Acknowledgments

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Anaesthesia, 1987, Volume 42, pages 757–759

CASE REPORT

Brachial plexus block

Unilateral thoraco-abdominal blockade following the supraclavicular approach

A. R. MANARA*

Summary

A supraclavicular brachial plexus block was performed which resulted in unilateral sensory and motor blockade of the thoracic and abdominal walls. General anaesthesia was therefore used and postoperatively it was noticed that analgesia of the upper limb had developed. It is likely that the blockade resulted from an intrapleural injection of local anaesthetic.

Key words

Anaesthetic techniques, regional; brachial plexus.
Complications.

The adverse sequelae of supraclavicular brachial plexus block are well documented, but reported here is a complication that has not been described previously.

Case history

An 18-year-old, 67 kg, male student was admitted with lacerations of the ulnar side of his right hand associated with distal sensory loss in the right little finger and possible injury to the flexor tendons of the little finger. There were no other injuries. He gave no significant past medical history, did not take any regular medication and had no known allergies. It was decided to undertake repair of the tendon and nerve injuries and suture the lacerations using a regional analgesic technique; no premedication was prescribed.

A supraclavicular approach to the brachial plexus was used, as described by Eriksson.[1] A 22-gauge, 1.5-inch short bevel needle was inserted lateral to the pulsations of the subclavian artery until contact was made with the first rib. It was then 'walked along' the rib until the patient complained of paraesthesiae around the elbow region. The needle was steadied, a 'T' extension set (Abbot) attached to the hub and, after careful aspiration, 15 ml 1.5% lignogaine with 1:200 000 adrenaline were injected, followed by 15 ml 0.5% plain bupivacaine. At no point in the procedure did the patient cough or complain of chest pain.

A right Horner's syndrome developed after 5 minutes and this was considered to indicate correct placement of the local anaesthetic solution. There was still full motor power at 25 minutes and no sensory impairment in the upper limb other than loss to pinprick sensation over the posterior aspect of the elbow joint. However, at this point the patient volunteered that his chest and abdomen were numb. On sensory

A.R. Manara, MB, BCh, MRCP, FFARCS, Research Registrar, Department of Anaesthetics, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

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testing there was complete unilateral anaesthesia to pinprick from T_4 to T_{12} along the right side of the anterior chest and abdominal walls. It was also noted that there was motor blockade of the right intercostal and abdominal wall muscles; the right side of the chest did not rise on deep inspiration and the right abdominal muscles did not tense on coughing. He did not complain of dyspnoea and, on auscultation, the breath sounds were normal and equal on both sides. The pulse and arterial pressure remained stable throughout the procedure. There was no further extension of the block of the trunk and still no evidence of any significant block in the upper limb after a further 10 minutes. At this point it was decided to proceed to general anaesthesia. This was induced with thiopentone and maintained with halothane and nitrous oxide in 30% oxygen, and the patient breathed spontaneously. The surgery lasted one hour and was uneventful.

The extent of analgesia was re-assessed in the recovery room, where it was found that anaesthesia and motor block of the upper limb had developed, as far as could be tested in the presence of a plaster of Paris back slab. The chest and abdominal anaesthesia were still present. There was no further extension of the block and full sensation and motor power had returned by the following morning except to the area supplied by the repaired digital nerve. At no point were there any symptoms or clinical signs suggestive of a pneumothorax. He made a full recovery and was discharged from hospital within a day.

Discussion

Brachial plexus block is a useful technique for upper limb surgery. However, it does carry specific risks. Bilateral blocks,[2] epidural anaesthesia,[3] subarachnoid block[4] and permanent neurological damage[5] have all been reported following an interscalene approach, but the main problems associated with the supraclavicular route are pneumothorax and intravascular injection of local anaesthetic. No reports of extensive unilateral trunk anaesthesia following a supraclavicular approach were found using a computer-assisted search of the literature.

The brachial plexus is enclosed in a continuous neurovascular fascial sheath that extends from the roots to the terminal nerves. The divisions of the plexus are in close relationship to the subclavian artery as it passes over the first rib; the artery is separated from the cervical pleura by Sibson's suprapleural membrane. During the performance of this block, the needle probably crossed the brachial plexus sheath and went on to pierce the suprapleural membrane at its attachment to the internal border of the first rib. The injected local anaesthetic solution then tracked along one of two directions. Firstly, it may have tracked between the chest wall and the parietal pleura and blocked the intercostal nerves in the thoracic paravertebral spaces. This is similar to the reported spread of India ink following the introduction of an epidural catheter into an intercostal space in cadavers.[6] Local anaesthetic would then be spread preferentially caudally rather than cephalad by the posterior attachment of the suprapleural membrane to the anterior border of the transverse process of C_7.

The second possible explanation is that after the needle had pierced the suprapleural membrane, it went on to pierce the cervical pleura and local anaesthetic solution was injected intrapleurally.

The spread of 30 ml of methylene blue dye was studied in cadavers to ascertain the more likely explanation. The brachial plexus, subclavian artery and suprapleural membrane were identified. A 21-gauge, 1.5-inch needle was used to pierce the suprapleural membrane just lateral to the artery at the midclavicular point and the dye injected. It proved impossible to inject dye between the suprapleural membrane and the pleura; the dye was injected intrapleurally on three separate occasions and coated the whole of the parietal and visceral pleura.

The most probable explanation for the anaesthesia in the reported case is, therefore, an intrapleural injection of local anaesthetic which led to widespread unilateral intercostal nerve block. Intrapleural blockade has been used to provide both intra-operative and postoperative analgesia for upper abdominal surgery.[7,8]

Caution should be exercised in the use of nitrous oxide should it be necessary to proceed to general anaesthesia following a failed supraclavicular brachial plexus block. The incidence of pneumothorax has been reported to be between 0.6 and 25% in patients following supraclavicular brachial plexus block; clinical features are delayed for 2–6 hours[9] and pneumothorax is more likely to follow a difficult block. The

administration of nitrous oxide increases the volume and pressure in a pneumothorax. The use of nitrous oxide following a failed supraclavicular brachial plexus block, is not absolutely contraindicated but the increasing availability of medical air should make its use unnecessary.

Acknowledgments

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CASE REPORT

Fatal disseminated intravascular coagulation following a monoamine oxidase inhibitor/tricyclic interaction

R. M. TACKLEY AND B. TREGASKIS

Summary

In spite of intensive therapy, an otherwise fit 34-year-old man died following the hyperpyrexial reaction to an interaction between tranylcypromine and clomipramine. There was no evidence of drug overdose, but severe disseminated intravascular coagulation developed which proved fatal.

Key words

Interaction, drug; tranylcypromine, clomipramine.
Hyperthermia.

Combinations of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have been used for many years in the treatment of refractory depression.[1] In the 1960s there were many reports[2,3] of severe adverse reactions to the combination, which included some fatalities. These occurred in particular when imipramine was added after MAOI therapy had been established. This type of combination therapy was reviewed by Goldberg and Thornton,[4] who considered that the risks can be minimised if certain precautions are taken and that the results can be worthwhile.

We report the case of a man who died following administration of a combination of clomipramine and tranylcypromine. At least four previous deaths due to combinations of clomipramine and MAOIs have been noted.[5]

Case history

A physically healthy, 34-year-old engineer had suffered from depression intermittently for 5 years which was treated with tranylcypromine (Parnate). Two days before admission, 10 mg clomipramine (Anafranil) was added twice daily because of failure of tranylcypromine alone to cure his depression, and the development of suicidal tendencies. He took the first capsule without ill effect but 3 hours after he took the second capsule as prescribed (some 30 hours prior to admission), he developed nausea and profuse sweating. The patient's general practitioner was consulted by telephone and the patient was reassured and told to continue with the medication. The patient did continue to take the capsules as prescribed and, after three more, he became agitated and confused. The general practitioner made a home visit and found him pyrexial, dyspnoeic, confused and shivering.

On admission, his axillary temperature was 39.7°C and heart rate 160 beats/minute. It was not possible to measure his blood pressure initially because of lack of cooperation. His illness was quickly diagnosed as caused by a drug interaction and there was no evidence of over-

R.M. Tackley, MB, BS, FFARCS, Senior Registrar, B. Tregaskis,* MB, BS, MRCP, Medical Registrar, Treliske Hospital, Truro.
* Present address: Royal Victoria Hospital, 13 Craigleith Road, Edinburgh EH4 2DN.

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dose. On the advice of a Regional poisons unit, and to control his agitation, chlorpromazine 50 mg was administered intramuscularly. Additional oxygen was given by mask. Following this, his blood pressure was found to be 100/60 mmHg.

He was transferred to the intensive therapy unit (ITU) because of a decreasing level of consciousness 2 hours after admission. His rectal temperature was found to be 42.9°C. He was becoming cyanosed, hypotensive and comatose with marked muscle fasciculation and rigidity. Pupils were mid size, equal and non-reacting. Arterial blood gas analysis (breathing air) revealed a marked metabolic acidosis (pH 7.14, $P\text{CO}_2$ 4.8 kPa, $P\text{O}_2$ 14 kPa, HCO_3^- 12 mmol/litre, base excess −16.7 mmol/litre). Other blood values were haemoglobin 15.3 g/dl, white cell count 4.5×10^9/litre, platelets 388×10^9/litre, sodium 146 mmol/litre, potassium 5.7 mmol/litre, chloride 104 mmol/litre, urea 10.6 mmol/litre, creatinine 279 μmol/litre. Immediate therapy began with rapid cooling with ice packs, fanning and wet sheets which brought the temperature down to 40°C within 2 hours and to 38.5°C one hour later; insertion of a central venous pressure line for measurement and for rapid infusion of cool fluids; 200 mmol of sodium bicarbonate (8.4%) which increased the base excess to +1 mmol/litre; tracheal intubation facilitated by etomidate, suxamethonium and alcuronium and positive pressure ventilation because of increasing arterial $P\text{CO}_2$; and frusemide 100 mg (+250 mg later) and 250 ml mannitol 10% because the patient had become oliguric.

Blood pressure was maintained at between 80 and 90 mmHg systolic with a central venous pressure of 9–15 cm H_2O, and the heart rate decreased gradually to 110 beats/minute. He became normothermic but examination of his central nervous system revealed unreactive pupils. Later in the night it was noticed that his abdomen was more tense, his intravenous sites had begun to ooze blood-stained tissue fluid and the blood pressure was decreasing. A nasogastric tube was passed and 1000 ml of blood aspirated from his stomach.

A full blood count and clotting screen revealed a haemoglobin of 6 g/dl, a platelet count of 38×10^9/litre, a prothrombin time of >5 minutes, a partial thromboplastin time of >5 minutes and a fibrinogen level of 0.1 g/litre. Disseminated intravascular coagulation (DIC) was diagnosed and later confirmed when a level of fibrin degradation products greater than 640 μg/ml was found. He was treated with blood, calcium, fresh frozen plasma and platelets. Increasing dobutamine and dopamine infusions failed to maintain an adequate blood pressure and the patient died 30 hours after admission.

Post mortem revealed a large retroperitoneal haematoma, 3 litres of bloody peritoneal fluid, large bloody pleural effusions, a small pericardial effusion and multiple small haemorrhages throughout the other organs including the brain. There was no evidence of pontine haemorrhage.

Discussion

This case is not unique in the literature[6–9] except for the development of DIC, which is not a reported complication of this interaction but can follow hyperpyrexias from other causes. However, we consider it valuable to draw attention to the hazards of combinations of MAOI and TCA drugs and to underline the advice about their use. In addition, the illness caused by the interaction may progress to death more rapidly than concrete information regarding its treatment can be found. Our experience may be of value to others.

Combinations of MAOI and TCA drugs are acknowledged to be hazardous; the combination of clomipramine and MAOIs is especially so.[10,11] Combination therapy may not be a wise first choice[1] but instances exist where improvement in the psychiatric condition may be expected. These include depressive illness where the risk of suicide may outweigh the risks of therapy.

The likelihood of severe or fatal interactions can be minimised by the avoidance of certain drugs of the TCA family such as imipramine and clomipramine, and the MAOI tranylcypromine[12] which has amphetamine-like properties. MAOIs can be divided into two groups according to their selectivity for inhibition of monoamine oxidase (MAO). MAO-A is found predominantly outside the central nervous system; MAO-B accounts for 80% of human brain MAO activity, and for that in the platelets. The use of a selective MAO-B inhibitor, such as Deprenyl, has been shown in animal studies to be safer than other MAOIs when used in combination with TCAs.[12,13] Fatalities in humans occur more

commonly when TCAs are added to an MAOI regimen than *vice versa*, but this has not been substantiated in animal studies.

The patient described in this report became rapidly hyperthermic following his admission to hospital and the resulting cerebral injury may have contributed to his death. The malignant hyperpyrexia syndrome associated with anaesthetic agents is muscular in origin. The chance of that mechanism underlying this pyrexia seems slight. Suxamethonium is a well-known trigger agent in individuals susceptible to malignant hyperpyrexia, and may cause increased muscle tone, but in our patient it provided good muscle relaxation for tracheal intubation. In addition, the patient was pyrexial before suxamethonium administration. Hyperpyrexia is also found in the neuroleptic malignant syndrome and cases have been reported to the Committee on Safety of Medicines that involved TCAs. There is some evidence that the underlying pathophysiology may be the same in these two conditions.[14]

Animal studies have shown that the administration of tubocurarine prevents, or attenuates, the hyperpyrexia that results from MAOI and TCA interaction, presumably by reduction of muscle tone and promotion of vasodilatation. However, barbiturates also attenuate the pyrexia, which is thought to be triggered centrally via 5-hydroxytryptamine.[12] Thus it seems unlikely that dantrolene (which is used to reduce muscle contraction in malignant hyperpyrexia) would have been more beneficial in cooling the patient than muscle paralysis, vasodilators, surface cooling and cooled intravenous fluids. These methods have been suggested following animal studies,[1] and used successfully in humans.[15]

Large volumes of crystalloid and colloid solutions were needed to maintain the blood pressure before DIC developed. Pressor amines were not used initially because of the theoretical risk of a hypertensive crisis.[16] Chlorpromazine was used successfully to control agitation and is recommended by some authors.[4,17] Its α-adrenergic blocking properties almost certainly assisted vasodilatation and cooling, but may also have contributed to hypotension which subsequently became difficult to treat. A hypertensive crisis did not occur with the inotropic drugs dopamine or dobutamine; these agents have very short plasma half-lives and could have been discontinued with rapid effect. In the presence of TCAs they should be started at one-tenth of the usual dose.[14] Systematically administered catecholamines are metabolised predominantly by the enzyme catechol-O-methyl transferase, and not MAO. Care should be taken, however, with amines that act indirectly such as ephedrine, which cause a release of amines from the nerve terminal.

DIC was most probably triggered by the high core temperature of 43°C, which alone could have been fatal. Earlier diagnosis before overt haemorrhage had started, and appropriate treatment with platelets and fresh frozen plasma, might have restored normal coagulation once the temperature had been controlled.

We conclude that the use of combinations of MAOI and TCA drugs may be justified under certain circumstances, but it is vital that the patient and medical attendants are aware of the possibility and symptoms of a drug interaction. A drug with greater cardiovascular stability than chlorpromazine should be used to control agitation when a drug interaction is diagnosed. Early, elective ventilation using non-depolarising muscle relaxants should help to correct acidosis, improve oxygenation and reduce the temperature increase. Sympathetic amines of the direct-acting type may be used cautiously in cases where there is hypotension. Haematological screening is recommended to predict DIC at an early stage.

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APPARATUS

A laryngoscope adaptor for difficult intubation

S. M. YENTIS

Summary

Tracheal intubation may be hindered by difficulty in insertion of the laryngoscope blade into the patient's mouth because the handle impinges on the patient's chest or on the hand of an assistant applying cricoid pressure. An adaptor is described which modifies the standard Penlon laryngoscope to enable lateral swivelling of the handle, thus avoiding the obstruction.

Key words

Equipment; laryngoscope.
Intubation; tracheal.

Insertion of the laryngoscope blade into the patient's mouth may be difficult due to impinging of the handle on the patient's chest. This may occur in the obese, in those with short necks or restricted neck and jaw movement, and especially in obstetric patients, when the breasts are enlarged. An assistant's hand applying cricoid pressure adds to the problem.

Various solutions have been suggested that range from detaching the laryngoscope blade from the handle before insertion [1] to modifications in laryngoscope design. The handle may

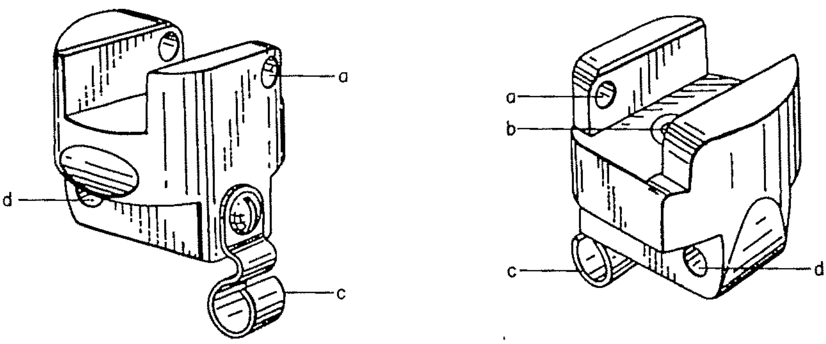

Fig. 1. The laryngoscope adaptor, seen from two different angles. (a) Hole for retaining screw, for attachment of blade to adaptor; (b) conducting rod; (c) retaining clip; (d) hole for retaining screw, for attachment of adaptor to handle.

S.M. Yentis, MB, BS, BSc, Senior House Officer, Department of Anaesthesia, Edgware General Hospital, Edgware, Middlesex HA8 0AD.

Present position: Senior House Officer, Department of Anaesthetics, Hammersmith Hospital, Du Cane Road, London W12 OH5.

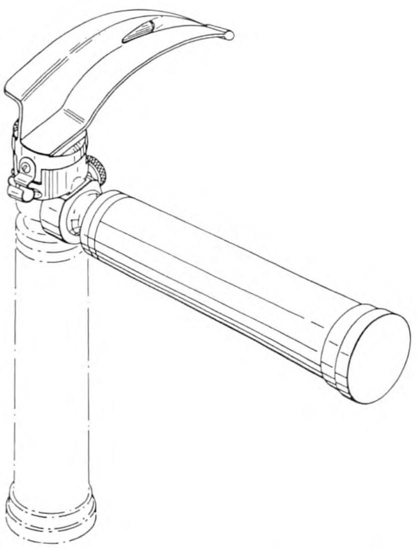

Fig. 2. Laryngoscope and adaptor assembled, showing lateral pivoting.

be shortened,[2] or the angle between the blade and handle increased. This widened angle can be adjustable[3] or fixed; examples of the latter are found in the polio laryngoscope which has a very obtuse angle[4] and in others which are angled less obtusely.[5,6]

However, visualisation of the larynx is easiest with the conventionally angled laryngoscope because it facilitates the application of force in the optimal direction. The adaptor described maintains the normal angle between handle and blade, whilst enabling easy insertion of the blade into the mouth.

Description and use of adaptor

The adaptor is a 2.5 × 2.5 × 2.5 cm block which fits between a standard screw-fit Penlon laryngoscope handle and Macintosh blade. It is made of a conducting metal and incorporates an insulated conducting rod which allows elec-

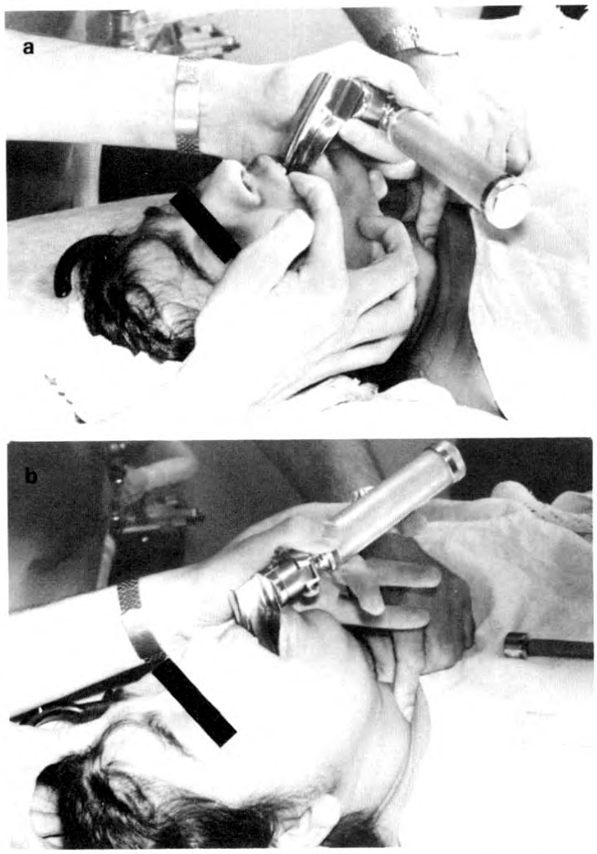

Fig. 3. The adaptor in use. (a) Insertion of the blade into the patient's mouth; (b) the handle in the normal position.

trical connexion between handle and blade (Fig. 1). The standard laryngoscope hinges in only one plane; the blade pivots upwards on the handle. This can still occur with the adaptor fitted but, in addition, there is lateral pivoting between blade and handle (Fig. 2).

This lateral pivoting allows the blade to be inserted into the patient's mouth with the handle pointing at 90° to the right, avoiding contact with the patient's chest or assistant's hand (Fig. 3(a)). The handle is swivelled back into the normal position, and the laryngoscope used in the normal way with the light on (Fig. 3).

The design of the adaptor with the handle on the right also enables the patient's trachea to be intubated in the left lateral position; here the handle will point vertically upward on insertion of the blade. The adaptor is easy to operate and fits standard screw-fit equipment; a modified form would adapt laryngoscopes with hook-foot fittings or those with fibreoptic connexions.

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Forum

Feedback during patient-controlled analgesia using a speech synthesiser

N. B. A. Hodsman, MB, ChB, FFARCS, G. N. C. Kenny, BSc, MD, FFARCS, Senior Lecturers, University Department of Anaesthesia, Glasgow Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER, G. W. A. Gillies, MB, ChB, FFARCS, Senior Registrar, Division of Anaesthesia, Victoria Infirmary, Langside Road, Glasgow G42 9TY, C. S. McArdle, MD, FRCS, Consultant Surgeon, University Department of Surgery, Glasgow Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER.

Summary

Patients who use on-demand analgesia prefer voice feedback rather than buzzer tones to indicate operation of the apparatus. Twenty-four patients had experience of a patient-controlled analgesia apparatus which incorporated a sophisticated feedback of buzzer tones and a speech synthesiser. Of those who expressed a preference, fifteen preferred the speech synthesiser and only one preferred the buzzer tones. The speech synthesiser is a reliable, inexpensive and simple method of supplying feedback to patients when such apparatus is used.

Key words

Pain; postoperative.
Equipment.

A study was undertaken to determine whether patients who use on-demand analgesia preferred a system that incorporates buzzer tones or speech feedback to indicate operation of the system. Patient-controlled analgesia (PCA) systems have been developed which use buzzer tones or a tape-loop system to indicate operation of the PCA apparatus. Both these systems have disadvantages, namely, poor patient comprehension for the former, and lack of reliability for the latter. A new technique for patient feedback is described which uses a speech synthesiser.

Our department has used a PCA apparatus over the last 2 years, based on an Apple IIe microcomputer, a computer-controlled IMED 929 infusion pump and a push button.[1] This has proved to be an effective, flexible and reliable system.

The apparatus was programmed to emit various tones when demands for analgesia were made, and patients were given instruction on the meaning of these tones before premedication. Whenever the patient felt pain, he had to press the push-button twice within 1 second. A single bleep was heard each time he pressed the button. If the demand for analgesia was successful, the apparatus would acknowledge this with a *series* of high-pitched bleeps. A low-pitched buzzing sound was emitted if the patient pressed the button during the lock-out period. However, if the patient pressed the button too slowly, apart from the single bleeps with each press of the button, there was no answering sound.

Patients did learn how to use the system satisfactorily with pre-operative teaching and postoperative assistance but many patients found it difficult to understand the various buzzer tones, especially in the early postoperative period.

Hull and Sibbald[2] reported experience of a tape-loop to provide feedback to the patient. They showed that patients did not require pre- and postoperative assistance if they were provided with verbal feedback. Attempts were made to incorporate their tape-loop into a commercially produced system, the Janssen ODAC apparatus,[3] but tape wear and unreliable tape drive systems forced these attempts to be abandoned and, at present, there are no commercial systems available with vocal feedback.

A Digitalker speech synthesiser was incorporated

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into the system in an attempt to make our PCA apparatus more acceptable to patients. This study was undertaken to determine patient preference for buzzer or vocal feedback.

Method

The Digitalker speech synthesiser kit consists of a speech processor chip, a speech read-only memory or ROM, an audio filter, amplifier, loudspeaker and an Apple-compatible board. The technique of time domain synthesis is used in the speech processor chip. A synthetic waveform is produced which sounds like the original speech waveform but, since exact reproduction of the original waveform would occupy a large amount of memory, time domain synthesis removes data which are not required.

The manufacturer records the original voice pattern, in this case that of an American male, onto a high-fidelity tape. The signals are then analysed by an elaborate computer program which generates a digital pattern for storage in the speech ROM. In the kit which we purchased, the master word list in the ROM contained 143 options: 136 words or letters, two tonic sounds, and five silent periods of varying duration to mimic the pauses between words in normal speech. The required words are obtained by placing the correct digital code for each word into a specific memory location on the Digitalker card and a simple program gave us these sentences. Firstly, 'Right, it's on'; the push button had been pressed correctly and an injection would be given. Secondly, 'Too slow, please try again'; although the button had been pressed twice, it had been pressed outside the 1-second time limit. Thirdly, 'Time limit, please wait *n* minutes'; the button had been pressed correctly but the demand for analgesia had occurred during the lock-out period and no analgesia could be given for *n* minutes.

The words available to us were somewhat limited because the options in the master word list were chosen by the manufacturers for a wide range of applications, and some improvisation had to be made. In this way, the word 'slow', which was not available on the word list, was formed by writing the program for the letter 's' plus the word 'low' with no pause between the two. The sound of the word produced was completely understandable. Similarly, the word 'wait' was not available on the word list, but the homonym 'weight' was.

The study

Twenty-six patients were entered into the study. They were aged 21–78 years and were scheduled to undergo elective abdominal surgery. They used PCA for the first 4 hours postoperatively: 2 hours with the speech synthesiser and 2 hours with the buzzer tones. They were allocated randomly to use one of these systems first: group 1 was allocated to use the speech synthesiser first, while group 2 used the buzzer tones first. The patients were kept in the recovery area for the duration of the study to avoid disturbing other patients in their wards, because the voice was rather loud and we had no earphones. The groups were comparable for age, weight and sex.

A standardised anaesthetic was prescribed: temazepam 20–30 mg was given orally as premedication. Anaesthesia was induced with thiopentone and maintained with nitrous oxide, oxygen and halothane or enflurane with increments of vecuronium or atracurium as required. Morphine was used intra-operatively and also postoperatively in the PCA apparatus.

Patients were asked at the end of the study and 24 hours later, which system they preferred and whether they had any comments about each system. It was initially intended to ask the nursing staff for their comments; however, owing to a staffing crisis all but five of the patients were recovered by one of the authors (N.B.A.H.).

Of the 26 patients who were entered into the study, two were withdrawn, one because she required re-operation, the other because she did not require analgesia during the study period. Table 1 shows the results from the remaining twenty-four patients.

Results

Of the patients who expressed a preference, fifteen preferred the speech synthesiser and only one preferred

Table 1. Results of patient preference for group 1 (vocal feedback first) and group 2 (buzzer feedback first).

	Preference			
	Speech	Buzzer	None	No memory
Group 1	5	1	2	4
Group 2	10	0	1	1

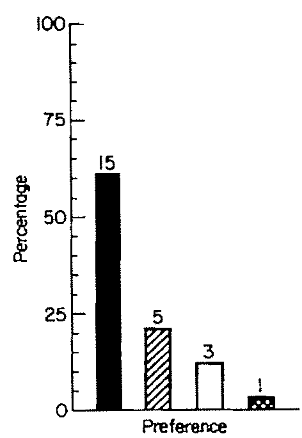

Fig. 1. Preference of patients for vocal or buzzer tone feedback. ■, Voice preferred; ▨, no memory of voice; □, no preference; ▩, buzzer tones preferred. Numbers at top of each bar indicate actual number of patients.

the buzzer tones. Three patients expressed no preference. The last group of five patients did not remember having heard the voice at all (Fig. 1). The numbers were too small for valid statistical analysis.

Discussion

The finding that five patients did not remember having heard the voice may be explained in part by the fact that four of them had been allocated to group 1 and had heard the speech synthesiser first. They would therefore still be recovering from the residual effects of anaesthesia. However, three of these five patients were said by the nursing staff to have understood the voice better, since on hearing 'Too slow, please try again', they did just that, whereas they did not respond in a similar way to the buzzer system.

We were unsure how patients would react to the rather monotonous American voice. We discovered very quickly that the nurses found it irritating and would have preferred at least a British voice. However, none of the patients complained about the voice and some even found it pleasant, soothing or amusing. Patients who were partially deaf found the voice easier to hear and understand. One patient had an interesting comment to make about the buzzer tones. She did not find the buzzer tones difficult to understand, because she had a home computer. Further questioning revealed that the tone used in our system to indicate that an injection would be given, was the same as that used in her home computer games for 'You're winning'.

Commercially available systems provide little feedback for the patient to indicate whether the patient is receiving an injection or if a demand has been made during the lock-out period. The ODAC system uses only a bleeping sound when the push button has been pressed, and the only way that the patient has of knowing that he has made a successful demand for analgesia is by the sound of the pump machinery working.

A sophisticated system of buzzer tones was incorporated into the apparatus used in our department, in an attempt to overcome the obvious problems for the patients in trying to cope with this lack of feedback. Patients still found it difficult to understand the different tones even with this addition.

The incorporation of the speech synthesiser into the PCA apparatus greatly improved the feedback to the patient and proved to be a simple, flexible and inexpensive system. It was also preferred by the majority of patients and would seem to offer an advantage over simple buzzer tones to provide feedback for PCA.

Acknowledgments

We thank Mr F. Toal, MIAP, for his assistance in the programming of the speech synthesiser and the PCA apparatus.

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Correspondence

Smoking and anaesthesia

The Association of Anaesthetists of Great Britain and Ireland and the Health Education Council should be congratulated on taking steps to provide pre-operative advice for patients who smoke (*Anaesthesia* 1987; **42:** 1–2). There can be little doubt that this aspect of anaesthetic practice has been a missed opportunity and that steps to decrease the impact of smoking on post-operative morbidity are long overdue. It should also

All correspondence should be addressed to Dr J. N. Lunn, Editor of *Anaesthesia*, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, United Kingdom.

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be said that we, as anaesthetists, have consistently failed to use our influence on patients to alter their long-term smoking habits. This is the clear conclusion from a regional survey into the anaesthetic management of patients who smoke, the final results of which confirm the initial trends, published recently.[1]

Questionnaires were circulated to 300 anaesthetists in the South Western Region and 174 were returned, a response rate of 58%. Only one anaesthetist did not feel that there was an association between smoking and anaesthetic morbidity and this awareness of the risks of smoking was further shown by the fact that 42% of the respondents had smoked regularly in the past but only 9% still did so at the time of the survey. Furthermore, 91% always or usually felt it necessary to ask patients pre-operatively, if they smoked. Despite this, 42% of the respondents never or only occasionally advised patients to quit smoking permanently and 45% never or only occasionally asked patients to abstain pre-operatively. When asked what might be the minimum period of abstinence that reduces anaesthetic risk, there was a wide spectrum of responses ranging from 2 hours to 6 months; no one period was chosen by the majority.

A frequent comment during the survey was that there was not enough time pre-operatively to make it worthwhile to advise patients to stop smoking. This observation is not valid in terms of the cardiovascular risk but, as regards decreasing the effect of smoking on other body systems, to make contact with patients months before their operations is obviously less feasible on an individual basis. It is to be hoped that the trial of pre-operative advice being undertaken will therefore get to patients early, since the major respiratory benefits of pre-operative abstinence from smoking have been shown to arise only after 2 months.[2] A particular target group might be those patients who are entered on waiting lists of more than 2 months' duration.

Morriston Hospital, C.C. CALLANDER
Swansea SA6 6NL

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The editorial on smoking and anaesthesia cannot be faulted in the conclusions it reaches, especially as concerns smoking education among the young. However, most practising anaesthetists would recognise two problems which must be addressed. The first of these is the problem of patients who come in for operation and are seen the day prior to going to theatre after they have been forbidden to smoke. They are usually in a very unstable psychological condition, they cannot sleep, they cannot eat and they have the full spectrum of withdrawal symptoms, which makes pre-operative sedation a very difficult exercise. The second problem is the 'tight chest'. Most people who are heavy smokers find it very difficult to expectorate when they stop suddenly, and to clear their chest of mucus until they have their first cigarette of the day. They arrive in theatre under these circumstances apprehensive, dyspnoeic and with a chest full of mucopus.

Faced with these problems the writer takes the easy route and allows people who have smoked until admission to continue to smoke, although advising them that this is a good opportunity for them to give the habit up. If I did not do this and cancelled the operations on all patients who refuse to give up cigarettes then our operating lists would be decimated and the bed wastage would be quite considerable.

It seems to me, therefore, that we have a choice of making sure our patients stop smoking at least 4 weeks prior to operation, if necessary in very major surgery by admitting them for detoxification in a controlled environment, or in the case of minor or intermediate surgery allowing them to continue smoking up to the day of operation. This may seem therapeutic nihilism to the purist but it is practical politics in the rough and tumble of day-to-day anaesthesia.

Inverclyde Royal Hospital, S. MCKECHNIE
Greenock PA16 OXN

A reply

We were very interested to read the letters from Dr Callander and Dr McKechnie concerning our editorial on smoking and anaesthesia and the Association's plans to increase awareness of the hazards of smoking in surgical patients.

The survey carried out by Dr Callander has yielded some very interesting observations concerning the current attitude of anaesthetists to this topic. There are obviously some problems with getting the right advice to the right patients at the right time but the Association's campaign, currently underway, aims to solve at least some of these and, as your correspondent rightly points out, any period of abstinence is better than none. We agree that the period of abstinence needed greatly to influence postoperative respiratory morbidity is measured in weeks rather than days, but the figure of 2 months quoted by Dr Callander and based on the work of Warner and colleagues,[1] may be rather long. Even a few days' abstinence greatly improves ciliary beating and one or two weeks provide a significant reduction in sputum volume.[2]

Dr McKechnie has drawn attention to a situation that, we agree, is not uncommon in medicine in general

and anaesthesia in particular; on occasion there appears to be a gap between acting on advice based on theoretical grounds and what is practically possible in the 'rough and tumble of day-to-day anaesthesia'. In the case of the smoker who comes to surgery, however, we are certain that the gap is either small or nonexistent. It would be a pity if the advice put forward by your correspondent, which is based on no scientifically supported (or supportable) observations, became regarded as a reasonable point of view within the profession. Two points are made, which are used to support the contention that for minor or intermediate surgery smokers should be allowed to continue to smoke up to the day of operation. The first concerns the psychological state of the patient and the second, the heavy smoker who is suddenly deprived of cigarettes and comes to theatre 'dyspnoeic and with a chest full of mucopus'.

Firstly, smoking is an addictive process and cessation may undoubtedly be followed by a withdrawal syndrome, but it differs in intensity and quality between subjects.[3] However, to state that, 'They are usually in a very unstable psychological condition, they cannot sleep, they cannot eat and they have the full spectrum of withdrawal symptoms ...' is not only an oversimplification but also an exaggeration of the situation. Indeed, it has been suggested[2] that because of the process of anxiety transference (from impending operation to giving up smoking) cessation is actually beneficial. Whether it is, or not, a comprehensive review conluded that there is no clear-cut association between pre-operative anxiety and surgical recovery.[4] Given the overwhelming evidence concerning the postoperative problems caused by pre-operative smoking and the fact that even a short period of abstinence lessens these, it is misguided to suggest that patients should not stop because of psychological reasons.

Secondly, it is again an unwarranted exaggeration to state that heavy smokers who are deprived of their first cigarette of the day arrive in theatre '... dyspnoeic and with a chest full of mucopus'. There is no doubt that, on cessation, some smokers report a transient increase in sputum volume and others that expectoration is difficult. To what extent these are real or imagined is difficult to say but there is no evidence that this is clinically a problem and reports generally agree that ciliary activity actually improves on cessation of smoking.[2-5]

Finally, we believe that it is quite wrong to differentiate the risks of anaesthesia in smokers according to whether surgery is major rather than intermediate or minor, and for patients who present for the latter to be given different advice. Regardless of the nature of the surgery, a cigarette smoker is at an increased risk. This risk is lessened the longer that smoking is stopped before surgery and although there are risks and benefits to be gained from most things in life, there can be no doubt that in this situation the benefits far outweigh the risk.

Guy's Hospital, R.M. JONES
London SE1
Association of Anaesthetists M. ROSEN
of Great Britain and Ireland,
9 Bedford Square,
London WC1 3RA

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Rapid inhalation induction

Wilton and Thomas (*Anaesthesia* 1986; **41**: 472–6) reported their use of single breath induction in adult outpatients. Based on over 100 cases in Scotland and Hong Kong, I offer some observations on breathing technique, the use of enflurane as an alternative to halothane, and the most appropriate carrier gas mixture.

Ruffle *et al.*[1,2] described single breath and triple breath techniques and found the latter to be more rapid. It is usually easy for patients to understand the instruction: take three very big, slow breaths in and out. Continued verbal encouragement improves the quality of induction.

Enflurane is preferable to halothane in my experience of more than 60 patients. The duration and quality of induction appear similar with either agent. Enflurane has a pungent smell but is not unacceptable.

The major determinant of induction rate and quality is the volume of anaesthetic inspired. Induction is slower and more eventful if patients fail to take maxi-

mal breaths as directed. It was suggested that nitrous oxide may cause a stage of excitement (G.B. Drummond, personal communication). To test this hypothesis, a randomised, blind study of 30 Cantonese-speaking women who were to have tubal ligation surgery was made. Inhalational induction with enflurane 5% either in 100% oxygen or in 70% nitrous oxide in oxygen was given. Fresh gas flows were set and monitored by a skilled assistant. Flowmeters were hidden from my view. Audio recordings with a live commentary on each induction were analysed on completion of the study.

Three patients refused the mask and were given an intravenous agent. Four patients breathed maximally from the start and had rapid, uneventful inductions; the onset of sleep was slower in those who breathed 100% oxygen but an analgesic state was reached in less than 4 minutes. Twenty-three patients (12 nitrous oxide, 11 oxygen) were judged to have breathed sub-optimally from the start. Rapid arm movements, breath-holding and trismus with poor airway patency occurred almost exclusively in those who breathed nitrous oxide in oxygen. Swallowing movements, with continued ventilation, and slow flexion of the limbs were seen in the oxygen group. Nitrous oxide caused more rapid loss of consciousness at the risk of impaired subsequent ventilation.

Initial, voluntary ventilation may be less than maximal during rapid inhalation induction with halothane or enflurane. Nitrous oxide should not be used unless full patient cooperation is guaranteed.

Prince of Wales Hospital, D.W. GALLOWAY
Sha Tin,
New Territories,
Hong Kong

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A reply

Thank you for the opportunity to reply to this letter and to discuss some of the points that arise from it. We agree that the volume of inspired anaesthetic agent is the major determinant of induction rate because the greater the volume inspired, the greater will be the alveolar concentration. We would also agree that a triple breath technique allows a greater volume of anaesthetic agent to be inspired and thus increases the alveolar concentration.[1] In our study a single breath technique was used since it was the simplest instruction that could be given to the patient and we were concerned that repetitive breaths with high concentrations of an inhalational agent might produce airway irritation and decrease patient compliance.

We considered a single breath induction technique with enflurane but found it to be too pungent for use in the manner we described with halothane. The few patients we attempted to induce with 5% enflurane had problems with either airway irritability or excitement during induction so we did not proceed with a formal study.

It is interesting that 23 (77%) of the 30 patients induced with the technique described in the letter above had some evidence of excitement, whereas only 14% of our patients exhibited similar problems. We suspect that this is because enflurane, a less potent anaesthetic agent than halothane, tends to produce a slower induction (with greater risk of an excitatory phase) if similar concentrations are used. Enflurane 5% is only approximately 3 × minimum alveolar concentration (MAC) of that agent, whereas the 4% halothane used in our study is equal to approximately 5 × MAC of that agent.[2] There is a considerable inspired-to-alveolar concentration gradient during inhalational induction of anaesthesia such that even after three breaths the alveolar concentration will be much less than the inspired concentration. Continued uptake from the alveoli tends to decrease the alveolar concentration further. A high inspired concentration of anaesthetic agent is thus required to produce a reasonable alveolar concentration if induction is to proceed swiftly.

Nitrous oxide was included in our technique to speed the induction and to minimise any excitatory phase that may occur during induction. Nitrous oxide should be of significant benefit since it contributes to the depth of anaesthesia and increases the uptake of the more potent anaesthetic agent by the second gas effect.[3] We cannot explain the different manifestation of excitatory phenomena in those patients in whom nitrous oxide was used and those in whom it was not, but do note that the incidence of these phenomena was similar in both groups. We suspect from the information presented in the letter that the use of a less potent, more pungent inhalational agent may be the primary reason for the excitatory effects seen.

If we had observed excitatory phenomena in 77% of our patients we would not have thought the technique could be offered as an alternative to intravenous anaesthesia. Furthermore, as we concluded in our paper, this form of induction should be undertaken only if the patient is completely cooperative.

Mott Children's Hospital, N.C.T. WILTON
Room C4139, V.L. THOMAS
Box 0800,
Ann Arbor,
MI 48109,
USA

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Use of volatile anaesthetics in the New World

The letter by Dr T.H.S. Burns (*Anaesthesia* 1987; **42:** 76) concerning unexplained hepatitis following halothane (UHFH), prompts us to comment on the use of volatile anaesthetics in North America.

In our view, two factors influence the choice of volatile agents in our environment. Firstly, UHFH is accepted from the medicolegal point of view despite the lack of objective data to establish its mechanism. Indeed, it is unlikely that an expert witness could now be found to defend an anaesthetist who had given repeated halothane followed by UHFH, unless the risk had been explained to the patient and their consent to further halothane recorded. This medicolegal position has evolved even though no case of halothane hepatitis has been settled in open court. Secondly, two other volatile agents (enflurane and isoflurane) are available in many North American centres without restriction in relation to availability of vaporizers or to cost. Many non-anaesthetists regard these agents as interchangeable with halothane and point to the lack of reports of unexplained hepatitis following their use. This is not quite the case[1,2] although the incidence of hepatitis is extremely low and, as yet, is not recognised in either a clinical or medicolegal setting.

A review of anaesthetic practice in our hospital over the past 5 years reveals how the factors outlined above have had their effect. In 1982, before the introduction of isoflurane, 85% of anaesthetics where a volatile agent was part of the technique would have included halothane and the remainder, enflurane. Isoflurane accounted for some 50% of anaesthetics one year after its universal availability and it accounts for 85% today, with the remainder divided between enflurane and halothane. Our use of these latter agents is now so small that we are unable to contract for a competitive price.

Our change in anaesthetic practice with regard to volatile agents appears to have occurred even though Canada is not plagued by the same medicolegal climate as prevails in the United States and our anaesthetic departments do not have unlimited budgets. Nevertheless, practice has changed in both countries and, in our view, is unlikely to revert to the pre-isoflurane era unless some serious side effect of this drug emerges. It may, therefore, become increasingly difficult to defend the continued use of enflurane or halothane against a background of clinical practice where these drugs are rarely employed.

Foothills Hospital
at the University of Calgary,
1403 29th Street NW,
Calgary T2N 2T9,
Alberta, Canada

L. Strunin
J.M. Davies

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Quality of axillary brachial plexus block

The paper by Dr Tuominen *et al.* (*Anaesthesia* 1987; **42:** 20–2) was interesting and requires some comment.

They have shown that peripheral nerve stimulators do not significantly improve the success rate of axillary brachial plexus blocks and are obviously surprised by this fact. However, their own retrospective survey did indicate this and they correctly quote Vester-Andersen's study[1] which had a success rate of 100% when a peripheral nerve stimulator was not used.

Why use nerve stimulators for this block? There is no doubt that these devices contribute to the success rate of other blocks, for example the classical approach to the sciatic nerve and supraclavicular brachial plexus blocks, but only because it is important that paraesthesiae be elicited for these blocks to succeed.

There are other blocks where the needle can be positioned in a neurovascular compartment without necessarily being near the nerve, for example the anterior approach to the sciatic nerve[2] and the classical axillary plexus block as described by Winnie.[3] In experienced hands a definite pop or loss of resistance can be felt when the needle passes into the neurovascular compartment and a large volume of local anaesthetic can then be injected. There is no need to use a nerve stimulator. Indeed, if one is used and the needle point is constantly adjusted to produce maximal muscle stimulation or paraesthesiae with the minimal current, then is there not a risk of the needle hitting the nerve with resultant damage? Working independently, Selander *et al.*[4] and Plevak *et al.*[5] showed that the incidence of nerve damage following axillary brachial plexus block was 3.5 times higher if paraes-

thesiae were elicited than if the needle was placed in the neurovascular compartment.

Success rates for many blocks vary from operator to operator but perhaps, now that Dr Tuominen and his colleagues have demonstrated that peripheral nerve stimulators have nothing to add to axillary brachial plexus blocks, their use should be reserved for blocks that can benefit from them.

Not only are they unnecessary for some blocks but they may hinder others. McLain[6] compared a nerve stimulator with paraesthesiae when perfoming interscalene brachial plexus blocks and found the latter to be more successful.

Royal Hospital for Sick Children, L.R. McNicol
Yorkhill,
Glasgow G38SJ

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A reply

Thank you for the opportunity to answer Dr McNicol's comments on our paper (*Anaesthesia* 1987; **42:** 20–2).

Firstly, Dr McNicol asks why use nerve stimulators for axillary plexus block, on the basis of Vester-Andersen's study[1] where a 100% success rate was reached without a nerve stimulator. All the blockades in that particular study were carried out by one person with an optimum of training since he used this technique several times every day. We, with less experience, achieved a satisfactory clinical success rate in our study using a nerve stimulator and all failures that required supplementation with general anaesthesia occurred in the perivascular group.

Secondly, Dr McNicol has the impression that nerve damage can result both from a nerve stimulator and from paraesthesiae. Theoretically, the nerve stimulator and paraesthesia techniques are quite similar. However, paraesthesiae are elicited by hitting the nerve, which is often felt as pain. On the other hand, a nerve stimulator with low current gives a muscular response (usually without pain) already a few millimetres from the nerve. In principle, the nerve stimulator technique hardly differs from the short bevel needle technique recommended by Selander.[2]

Finally, we do not agree with Dr McNicol's recommendation that a nerve stimulator should be reserved for other than axillary plexus blocks. We feel that the nerve stimulator for an axillary plexus block is a useful device which contributes to the success rate especially in obese patients, in patients with contractures or when abnormalities in the shoulder region make identification of landmarks difficult. An uninterrupted training programme with the use of a nerve stimulator in regional anaesthesia is necessary for one to obtain sufficient skill.

Surgical Hospital, M. Tuominen
Helsinki University Central Hospital, P.H. Rosenberg
Kasarmikatu 11–13,
00130 Helsinki,
Finland

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1. Vester-Andersen T, Eriksen C, Christiansen C. Perivascular axillary block. III. Blockade following 40 ml of 0.5%, 1% or 1.5% mepivacaine with adrenaline. *Acta Anaesthesiologica Scandinavica* 1984; **28:** 95–8.
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Pressure–flow relationships in intravenous infusion systems

We would like to compliment Dr Kestin on his evaluation of flow through intravenous cannulae (*Anaesthesia* 1987; **42:** 67–70). His results confirm our analysis of intravenous infusion systems, in which we also demonstrated a nonlinear relationship between pressure (P) and flow (F) in plastic tubings, cannulae and other devices.[1,2] When flow is determined at multiple driving pressures, we found the relationship between P and F to fit the binomial equation $P = R_L F + R_T F^2$, where R_L and R_T are the coefficients of flow and the square of flow, respectively. This binomial relationship is valid for flows of 9.6–639 ml/minute generated by pressures of 0.26–51.9 kPa.[1] Reynolds numbers calculated from the experimental data were 81–5322; turbulent flow occurs in intravenous infusion systems even at very low Reynolds numbers.

A combination of laminar and turbulent flows appears to exist. The laminar (linear P–F) component correlates with pressure loss calculations obtained

using the Poiseuille equation. The turbulent-flow *P* loss in intravenous cannulae (due to F^2) is found to be the sum of entrance length flow disturbance, kinetic energy loss at the outflow and internal shape change losses.[2] In addition, we identified turbulent-flow *P* loss intrinsic to the intravenous tubing, which is proportional to tubing length and independent of entrance and exit flow phenomena.[1] Laminar and turbulent flow pressure losses due to the attached intravenous tubing must be considered in any evaluation of cannula performance.

We would like to emphasise the importance of the British standard for intravenous cannulae which includes a technique to determine, and therefore compare, flow rates. Appropriate infusion systems can then be designed or selected to meet specific clinical needs. We support the adoption of standards for intravenous infusion systems which utilise more than one pressure–flow determination. A single rate measurement at approximately 10 kPa can result in a considerable overestimation of flow in the range needed for volume resuscitation during surgery or after trauma.[3]

Bioengineering Laboratory, B.K. PHILIP
Department of Anesthesia, J.H. PHILIP
Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA 02115, USA

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A reply

Drs Philip and Philip have admirably evaluated the pressure–flow relationships in this administration set–cannula system as a whole. Using the Travenol blood administration set, under normal conditions of usage with the 500-ml infusion bag hung 1 metre above the cannula without pressure, the cannula size is always the rate limiting factor for all sizes of cannulae available in the United Kingdom. However, the flows with a 10-G cannula attached are reduced only marginally compared to the administration set alone, so any reduction in the bore of the administration set will result in the administration set becoming the rate limiting factor when large bore cannulae are used. This may be the case in the report by Drs Philip and Philip, which utilised administration sets with either 2.3 mm or 3 mm internal diameter.[1]

The flows and equations obtained through administration set–cannula systems together, therefore, depend on the bore of the administration set and the applied infusion pressure which may critically alter both the ratio of laminar to turbulent flow and the rate limiting site. The BS4843 flow determination (which is *not* obtained using an administration set) which is quoted on the packaging of intravenous cannulae can be taken only as a rough estimate of the clinically obtainable flow and is probably as satisfactory a method as any, given the multiplicity of other factors that determine how fast an intravenous infusion runs in any particular patient.

Denver Children's Hospital, I.G. KESTIN
1056 East 19th Avenue,
Denver, CO 80218, USA

Reference

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Carminative property of peppermint in magnesium trisilicate mixture, BP

Magnesium trisilicate mixture, BP is commonly used, especially in obstetric practice, to alkalinise gastric contents prophylactically against the acid aspiration syndrome. According to the *British Pharmacopoeia*,[1] the mixture contains concentrated peppermint emulsion 25 ml/litre, which is equivalent to 0.5 ml pure peppermint oil/litre. Peppermint oil is a carminative used in the treatment of flatulent dyspepsia and acts by relaxation of the lower oesophageal sphincter to allow oesophageal reflux. Sigmund and McNally[2] demonstrated this action experimentally in volunteers using intra-oesophageal, intragastric and intrasphincteric balloon manometry. They found that instillation of 30 ml diluted peppermint spirit into the stomach caused relaxation of the cardiac sphincter and equalisation of intragastric and intra-oesophageal pressures, with reflux in 25 out of 27 subjects within 1–7 minutes of administration. The sphincteric relaxation lasted approximately 30 seconds and was terminated by an oesophageal peristaltic wave.

Relaxation of the lower oesophageal sphincter at the time of induction of anaesthesia carries the risk of passive reflux of gastric contents and acid aspiration. It would thus appear sensible to avoid giving magnesium trisilicate mixture, BP shortly before the induction of anaesthesia: indeed, would not the use of

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an antacid without a carminative flavouring be more logical?

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Birmingham B152TH

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Modified Magill forceps for difficult tracheal intubation

We note the description by Pelimon and Simunovic (*Anaesthesia* 1987; **42:** 83) of a modification to the standard Magill forceps for intubation. In 1978, Dr H. Liberman[1] from this Department described a new intubating forceps in which the forceps applies an anteroposterior grasp on the tube instead of the traditional side to side grip of the Magill forceps. The jaws are smooth, not serrated like the Magill forceps, since the jaws on the Magill forceps frequently damaged the cuffs of tracheal tubes. Early attempts to achieve this grasp by turning sideways the ridged end jaws of the Magill forceps, were abandoned in favour of a sliding mechanism to open the two smooth jaws.

These forceps have now been in use in this hospital for over 10 years and a paediatric version has been particularly useful in the manipulation of tracheal tubes during nasotracheal intubation in premature and other neonates. The anteroposterior grip and the ability to manoeuvre the tip of the tube in a fore-and-aft direction are definite advantages of this type of forceps.

The Prince of Wales Hospital, J.B. VONWILLER
Randwick, NSW 2031, Australia H. LIBERMAN
E. MAVER

Reference

1. LIBERMAN H. A new intubating forceps. *Anaesthesia and Intensive Care* 1978; **6:** 162–3.

Passive or active scavenging systems?

We were interested to read the letter from Dr Railton and colleagues (*Anaesthesia* 1987; **42:** 86) about the servicing of Ohmeda active scavenging units.

In East Anglia over 200 non-active scavenging systems were installed over 10 years ago. These systems are either entirely passive with discharge to the atmosphere, or assisted passive with discharge via the extract duct of the theatre ventilation; in all cases a safety block is used as a collecting point.

We recently conducted a survey of the scavenging systems installed in every NHS hospital in the East Anglian Region. The disposal systems functioned in a satisfactory manner in every theatre which we tested and reduced the pollution by over 90%. The mean pollution level with the passive scavenging in use was below 25.0 p.p.m. nitrous oxide; with identical flows of nitrous oxide but without scavenging the mean level was 350 p.p.m. In one new theatre complex fitted with active scavenging, which worked correctly, the level of pollution under identical test conditions was again below 25 p.p.m. nitrous oxide.

We could find no evidence that the passive disposal systems had received any maintenance during their average 10-year life and, as they still functioned well, we again question the rationale for the installation of active systems. In addition to the increased cost of installation Dr Railton's letter highlights the cost of maintenance for such systems. Indeed, on the figures he quotes the additional service cost would be £6,200 a year and, at current prices, would have been £62,000 over the past 10 years.

The suggestion by Dr Railton and his colleagues that routine servicing be abandoned in favour of checking the flow rate and obtaining service exchange units when necessary, may improve the efficiency and reduce the revenue implications of active systems. However, with the normal non-recirculating theatre ventilation systems, it would probably still be cheaper and certainly as efficient to scrap the active systems and install passive disposal systems connected to the theatre extract ducts.

Addenbrooke's Hospital, R.M. KIPLING
Cambridge C629QQ D.W. BETHUNE

Cardiac dysrhythmia after subtrigonal phenol

We would like to report a complication of subtrigonal phenol injection therapy for severe incontinence.[1] The patient was an otherwise well 19-year-old Nigerian woman with urinary incontinence as a result of spina bifida.

Anaesthesia was induced with a sleep dose of thiopentone and maintained with 67% nitrous oxide and halothane in oxygen breathed spontaneously. Thirty millilitres of 6% aqueous phenol was injected at six separate sites through the bladder wall using a 20-G needle inserted down a cystoscope.

The electrocardiogram displayed frequent multi-

focal ventricular ectopics after the second last injection of 5 ml phenol, which resolved after a minute or so, and during this the blood pressure remained stable. It was decided to complete the procedure with a final injection of 5 ml phenol in another site; within 30 seconds the dysrhythmia returned, and again resolved spontaneously.

Cardiac dysrhythmias are the commonest systemic complication of phenol but such reports are usually associated with the use of at least 40% phenol, as in plastic surgery.[2,3] Cutaneous absorption with resulting toxicity is implicated.

Subtrigonal injection of phenol is reported as a safe technique[1] and we are unaware of any reports of systemic phenol toxicity that have resulted from this. The dysrhythmia developed in this case after injection at two separate sites so intravascular injection is an unlikely cause, although bladder hyperaemia may have increased systemic absorption.

Anaesthetists should be aware of this complication associated with the use of phenol.

Walton Hospital, T. FORREST
Rice Lane, D.T.O. RAMAGE
Liverpool L9 1AE

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Difficulty in extubation

We write in response to the letter by Dr Wood who experienced difficulty in extubation following the use of an RAE tracheal tube and a Boyle–Davis gag with the Doughty modification (*Anaesthesia* 1987; **42**: 220). We strongly suspect that this hazard is not inherent to this type of tracheal tube since we have experienced, along with others, a similar problem with different types of tracheal tubes. We drew attention[1] to the fact that certain batches of Doughty's modification of the Boyle–Davis gag did not conform to the manufacturer's specifications in that the slot was excessively wide. Furthermore, we suggested that because of the variation in external diameters and manufacturer's tolerances of the many types of tracheal tubes now available, the 76-mm blade should be used with all tracheal tubes up to and including the 5.5 mm internal diameter, regardless of the age of the child. This policy has eliminated the problem of herniation of the tube through the slot and has not reduced surgical access. It is of interest to note that Dr Wood experienced this problem using a tube of 5.5 mm internal diameter and an 89-mm Doughty-type blade.

Broadgreen Hospital, P.M. BUCKLEY
Liverpool
Alder Hey Children's Hospital, G.H. BUSH
Liverpool L12 2AP

Reference

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Risk of infection from water bath blood warmers

The warming of blood and blood products prior to transfusion is widely recommended and a variety of commercial blood warmers are available. The immersion of a coil in a heated water bath is the most common method but it is frequent practice to immerse the whole bag of blood or fresh frozen plasma in the water to avoid the increased deadspace of the coil. This practice was recommended since it was shown that it has no effect on the composition of the blood.[1]

In 1981 Casewell *et al.*[2] reported a case of fatal *Pseudomonas* septicaemia in a patient given fresh frozen plasma that was rewarmed in a theatre water bath that was heavily contaminated with *Pseudomonas aeruginosa*. They recommended that baths should be disinfected daily with chlorhexidine and refilled with sterile water and, whilst in use, they should be changed every 4 hours.

There are no strict guidelines for the care of water bath blood warmers but in our hospital they are emptied daily, cleaned, left dry overnight and refilled each morning with sterile water. It seems unlikely in a busy operating suite that they could be cleaned more frequently. We tested the water as a possible source of infection by sending for culture, samples from four water baths that had been in use for 8 hours each day for a week. The results were as follows: *Bacillus* species were grown in 72% of the samples, *Flavobacterium* species in 39% and *Pseudomonas* species in 9%.

It seems likely, therefore, that contamination of entry ports on blood bags, and of injection ports and joints when extension sets are used,[3] may occur with total immersion and this practice should not be recommended. Finally, in view of the potential risk to patients we should not use water bath blood warmers

at all but dry-heat exchangers of which there are several available commercially.

The Middlesex Hospital, London WIN 8AA B.M. Bray

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3. Vaghadia H. Blood warming with the Avon A60 extension set. *Anaesthesia* 1984; **39:** 932–3.

Contamination of ampoules

The recent account of a contaminated bupivacaine ampoule (*Anaesthesia* 1987; **42:** 87) was interesting. Many users have noticed similar flakes when ampoules are opened.

Ampoules of drugs are now coded with a white band of paint at the neck of the ampoule to indicate that it is not necessary to use a file to open the ampoule. However, flakes of this paint frequently contaminate the contents and although the larger pieces are easily seen, smaller fragments can be aspirated into the syringe and injected into patients. Radiologists have now rejected crack-open type ampoules in favour of ampoules enclosed by a resealable rubber diaphragm because of the danger from injection of small particles of glass or paint during angiography. Perhaps anaesthetists should also insist on this type of ampoule or use a filter needle when drawing up drugs.

Royal Hallamshire Hospital, Sheffield S10 2RX T. Kirkpatrick

Bain anaesthetic system, gender and obesity index

We were pleased to read the letter from Romano *et al.* (*Anaesthesia* 1986; **41:** 1263–4). They found that female patients required a lower fresh gas flow/kg/minute ($\dot{V}_{FG}$) than male patients to maintain similar $Paco_2$ during anaesthesia with a Bain anaesthetic system. They stated that this difference among the groups could have been due to a lowered physiological deadspace and carbon dioxide production in female patients. However, we would like to point out that obesity (obesity index = weight/height^2) also plays an important role in the determination of $Paco_2$ for a given $\dot{V}_{FG}$.

In a group of 32 female patients who underwent abdominal hysterectomy under general anaesthesia using a Bain anaesthetic system (V_T = 10 ml/kg, f = 12 breaths/minute, I:E = 1:2, $\dot{V}_{FG}$ = 100 ml/kg/minute), the $Paco_2$ at 20 minutes after the start of anaesthesia was 4.02 kPa (SEM 0.06). This value is lower than that reported by Henville and Adams,[1] 4.57 kPa (SD 0.6), in a group of males and females. We also found that for similar $\dot{V}_{FG}$ (100 ml/kg/minute), there was no correlation between $Paco_2$ and age, $Paco_2$ and height, or $Paco_2$ and body surface area. However, there was an inverse linear correlation between $Paco_2$ and weight, and between $Paco_2$ and obesity index. $Paco_2$ correlated better with obesity index ($r = 0.53$, $p < 0.01$) than with weight ($r = 0.35$, $p < 0.05$). When the patients were divided into two groups according to the obesity index (group I, patients with obesity index <30; group II, patients with obesity index >30), group II had significantly ($p < 0.001$) lower $Paco_2$ than in group I: 3.76 kPa (SE 0.11) and 4.15 kPa (SE 0.05), respectively. The two groups were similar in age distribution. Therefore, our results show that obesity index plays an important role in the determination of $Paco_2$ for a given $\dot{V}_{FG}$ in the Bain anaesthetic system and should be considered whenever a fine-tuning regulation of $Paco_2$ is mandatory. The authors (Romano *et al.*) did not state the weights of their groups and it is possible that there were more patients in the female group who had a higher obesity index than in the group with male patients.

Queen Elizabeth Hospital, University of West Indies, Barbados, West Indies

K.B. Shankar
H. Moseley
Y. Kumar
M. Ramasamy

1. Henville JD, Adams AP. The Bain anaesthetic system. *Anaesthesia* 1976; **31:** 247–56.

Extracorporeal shock wave lithotripsy

We have treated 1600 cases during the last 10 months and have used epidural anaesthesia at the level of L_1–L_2 with 20 ml lignocaine 2% without adrenaline.

Coagulation defects are usually considered to contraindicate extracorporeal shock wave lithotripsy under epidural anaesthesia but a recent patient was treated successfully. The patient was 35 years of age and suffered type B haemophilia and had a kidney

stone. Factor IX was given before the treatment and epidural anaesthesia was used. The operation lasted 35 minutes and 1700 shock waves were given without pain. There was no evidence for 10 days after of any epidural haematoma and no bleeding occurred apart from the usual slight haematuria. Provided that appropriate treatment can be given it appears from this single case that extracorporeal shock wave lithotripsy and epidural anaesthesia can be used safely.

Sismanoglion Hospital,
15 126 Marousi,
Athens,
Greece

G. ECONOMACOS
S. LOUKAS
D. MANTZOURATOS
C. DIMOPOULOS

Total collapse of lung and CPAP

A report of the use of continuous positive airway pressure (CPAP) via facemask in the successful treatment of persistent pneumothorax associated with post-traumatic lung contusion is in press. CPAP has been advocated previously in other situations where functional residual capacity and lung compliance are decreased, such as postoperative atelectasis.[1,2] We describe now a case of postoperative total lung collapse which was treated successfully by CPAP administered via facemask.

A 62-year-old man received elective ventilation of his lungs after a two-stage oesophagectomy with a right thoracotomy for carcinoma of the oesophagus. He smoked 20 cigarettes per day and lung function tests showed a mild obstructive defect. Chest X ray was normal and he was otherwise fit.

Ventilation was continued for 48 hours after return from theatre, a longer period than usual on account of a number of problems: persistent haemorrhage that necessitated a return to theatre for haemostasis, atrial fibrillation, and bronchospasm which required bronchodilator therapy. At the time of extubation his chest X ray demonstrated clear lung fields.

Examination of the chest 12 hours later revealed dullness over the left hemithorax with greatly reduced air entry. Chest X ray confirmed complete collapse of the left lung field. Blood gas analysis showed Pa_{O_2} 8.4 kPa on an inspired oxygen concentration of 43%.

In view of his adequate oxygenation and his alert and cooperative state, a trial of CPAP therapy was commenced with a tight-fitting facemask (Medic-Aid) and Ambu CPAP system with a positive pressure of 0.75 kPa for 30 minutes in every hour. He also received intensive physiotherapy 4 hourly. Repeat chest X ray after 12 hours of this regimen showed some re-expansion of the upper zone of the left lung and, by 24 hours, only slight basal collapse remained.

The therapy was continued for a further 48 hours with CPAP reduced to 30 minutes prior to physiotherapy. He was discharged to the ward on the fifth postoperative day where he made an uneventful further recovery.

One would not advocate this therapy in patients who are significantly hypoxaemic, or unable to cooperate fully and tolerate the mask or to cough, but this case demonstrates that CPAP can aid the re-expansion of major lung collapse and thus avoid the risks and discomfort of tracheal intubation, ventilation and bronchoscopy. It may well have a major part to play in the prophylaxis and early treatment of postoperative pulmonary atelectasis and merits further investigation with respect to optimum duration and frequency of application.

Ninewells Hospital,
Dundee DD1 9SY

C.A. DAVIES
I.S. GRANT

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The cricoid yoke

The paper by Lawes *et al.*[1] described a device to apply a measurable force to the cricoid cartilage which presupposed the validity of the measurements made by Wraight *et al.* (*Anaesthesia* 1983; **38:** 461–6). Dr T.H. Howells has kindly allowed me to examine the device used in the latter study. The applicator used to compress the tissues that overlie the cricoid was intended to represent the area covered by three fingers (T.H. Howells, personal communication) and was found to have a surface area of over 15 sq. cm, with an oval border. The applicator inevitably overlaps the cricoid cartilage above and below when it is in position. One possible consequence of this shape is dissipation of some of the force used against other tissues, notably the thyroid cartilage. This may explain the rather surprisingly high force they found necessary to achieve protection against regurgitation.

Using a laryngeal specimen from a fresh male adult cadaver, a force of 4.5 N, applied by the index finger to a thin-walled latex tube of 1 cm flattened diameter held against the posterior surface of the cricoid cartilage, was necessary to just occlude flow of saline in the tube at a pressure of 16 kPa. This is almost a tenth of the force recommended yet is sufficient to

occlude a soft tube that carries fluid at twice the maximum pressure likely to be encountered clinically. Casts of the larynx made in plaster of Paris indicate that the diameter of the compressed hypopharynx at cricoid level is likely to be about 3 cm. However, even if allowance is made for this there still remains a large discrepancy between recommended force and the force required experimentally. Should we perhaps repeat the original experiments of Wraight *et al.* using a cricoid applicator tailor-made to compress the cricoid and only the cricoid?

Newham General Hospital,
Plaistow, London E13
A.I.J. BRAIN

Reference

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A reply

Thank you for allowing me to comment on Dr Brain's letter. We agree that our applicator shape and area allowed some dissipation of force but the order of force we recommended (*Anaesthesia* 1983; **38**: 461–6) was similar to that employed by experienced anaesthetists who perform cricoid pressure in their clinical practice (*Anaesthesia* 1983; **38**: 457–60) using the three digit application method of Sellick.

Dr Brain's experiment that measured the occlusion of a thin latex tube pressed against the posterior surface of the cricoid cartilage of an isolated cadaver larynx, suggests a very small force is required. It may well be the case that the various intervening tissues in the neck do dissipate the cricoid force when applied in the usual manner, which I maintain should be to about 40 N. This force is not surprisingly high and one which I have tolerated for periods of 30 seconds on many occasions in the course of our work (my 16½-inch collar size may account for considerable intervening neck tissue). Dr Brain's suggested 4.5 N is probably the order of discomfort I experience when wearing a 16-inch collar but would be, in my view, quite insufficient a force to protect against regurgitation.

The Royal Free Hospital,
London NW3 2QG
T.H. HOWELLS

Accidental intra-arterial injection of propofol

The induction agent propofol has been in common use in the United Kingdom since June 1986. As yet, there does not appear to be a reported case of accidental intra-arterial injection (ICI, personal communication).

We report what may, therefore, be the first situation in which this has occurred. Four millilitres of the standard solution of propofol was injected into the left brachial artery of a 42-year-old woman for day case surgery. Blanching in an oval area 4 cm wide, 6 cm proximal and 4 cm distal to the point of injection occurred within 5 seconds. The patient cried out in agonising pain which was felt radiating from the injection site down the anterior aspect of the left forearm into the palm of the hand about 8–10 seconds after injection was commenced. The injection was stopped immediately and anaesthesia was induced using propofol in the other arm.

Postoperatively (half an hour after the first injection) we noted a hyperaemic appearance over the anterior aspect of the forearm and palm. Subjectively, the forearm and hand felt slightly stiff. Four hours later she had no complaints and she had no residual symptoms on questioning a week later. There was no functional deficit in the forearm or hand.

Bromley Hospital,
Bromley,
Kent BR2 9AJ
M. CHONG
T.P. DAVIS

Another hazard with the Penlon off-line vaporizer mounting system

The introduction of enflurane and isoflurane, combined with problems associated with the use of halothane, has led to an increase in the use of free-standing vaporizers. In order to overcome the problems of using vaporizers in this way[1] our department decided to change to an interchangeable vaporizer system. A trial of the Penlon off-line and the Ohmeda Selectatec was undertaken to decide our choice.

The provison of one isoflurane vaporizer for the trial meant that it had to be carried from the anaesthetic room to the operating room for each case in which it was used. The third case on a busy, all-day plastic surgery list was a block dissection of the groin.

A Penlon Oxford 200 ventilator and a Bain system were used. It proved extremely difficult to keep the patient's systolic blood pressure below 100 mmHg despite increasing concentrations of isoflurane. The patient started to demonstrate obvious signs of awareness after 20 minutes. A rapid check of the anaesthetic machine showed that the corrugated connecting tube from the back of the vaporizer had broken. This was not obvious from the front of the anaesthetic machine. The following day the patient was questioned to see if she had suffered any awareness during surgery; fortunately, she had not.

Controlled ventilation of the lungs of patients with

the Penlon Nuffield 200 and a Bain system disguises this type of disconnexion.[2] Moving vaporizers in the middle of busy operating lists vitiates the anaesthetic machine check carried out before the list starts.

Norfolk and Norwich Hospital,
Norwich

C.H.M. Woollam

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1. Kelly DA. Free-standing vaporizers. *Anaesthesia* 1985; **40**: 661–3.
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Possible safety hazard on anaesthetic machines

A recent incident highlights a potential failure in an anaesthetic machine which would not be detected by currently recommended pre-anaesthetic checks.

An Ohmeda Boyle 2000 anaesthetic machine was subjected to the usual pre-anaesthetic checks including a single gas test with the oxygen cylinder on and the oxygen hose unplugged from the wall supply. It was noticed that the oxygen *pipeline* pressure gauge showed a low pressure reading while the oxygen cylinder was on. Normally this gauge should remain at zero unless the oxygen hose is plugged into a wall outlet. Simultaneously a soft hissing sound was noticed. Investigation revealed that oxygen was flowing in a retrograde manner from the unplugged oxygen hose. The machine was immediately withdrawn from service.

As expected, the Ohmeda service engineer reported that the pipeline non-return valve had failed. The rubber O-ring which forms the seal to prevent reverse flow was replaced but the valve failed again one week later. The whole valve assembly was then replaced and there has been no further failure.

If the problem had not been noticed, and if there had been a failure of the hospital's compressed oxygen supply, then upon turning on the oxygen cylinder its contents would have discharged into the pipeline. This would have dangerously depleted the cylinder contents.

If the valve had failed to a lesser degree, so that no flow were audible from the hose probe and insufficient pressure developed in the hose to cause the gauge to move, then the failure would have gone undetected. On many slightly older models of Boyle's machine the lower pressure oxygen gauge shows system pressure rather than pipeline pressure. This should always show a value above zero when pressurised oxygen is present and so does not permit detection of the failure described.

In the course of routine servicing the engineer tests the pipeline non-return valve by means of a static pressure test of the machine system and by forming a bubble of soapy water over the pipeline probe and looking for an increase in its size. The routine pre-anaesthetic check, as usually described, does not include a test of the pipeline non-return valve, although failure could lead to a rapid loss of the oxygen supply. Feeling or listening for flow from the probe will not detect small leaks, although such leaks will deplete the cylinder only slowly. The use of saliva to form a bubble is not to be recommended as any particulate matter present could be blown through to jam the Rotameter needle valves. The only solution is to use the bubble test practised by the engineers.

University of Sheffield,
Beech Hill Road,
Sheffield S10 2RX

P.A. Bamber

Re-insertion of minitracheotomy

Minitracheotomy has established a useful role in the management of patients with sputum retention.[1] High frequency jet ventilation (HFJV) may be undertaken through a minitracheotomy in patients with respiratory failure without rendering the larynx incompetent.[2] Difficulties with cannula insertion may be encountered but this is a report of a complication which followed cannula replacement.

A 65-year-old man developed sputum retention and respiratory failure following surgery for a perforated colonic carcinoma. A minitracheotomy cannula (Portex) was inserted to facilitate tracheal toilet and HFJV was commenced by this route 5 days later (Bromsgrove Humidified Jet Ventilator; Penlon). After 2 days of HFJV at a rate of 160 breaths/minute and driving pressure 3.5 kPa there was increasing resistance to the passage of suction catheters through the cannula and partial blockage or kinking was suspected.

An introducer from a new Minitracheotomy insertion pack (Minitrach II; Portex) passed easily down the cannula which was removed and shown to be kinked. A new cannula was railroaded into position over the introducer and caused the patient to cough. Breath sounds were audible through the cannula; passage of a suction catheter caused further coughing and mucopurulent secretions were aspirated.

HFJV was resumed through the new cannula but the patient became acutely distressed within 20 seconds, with extensive surgical emphysema of the neck and supraclavicular fossae associated with central cyanosis and bradycardia. The jet was disconnected immediately, 100% oxygen administered by facemask and 0.6 mg atropine given intravenously. Respiration remained laboured so an oral 8.5 mm profile cuff tracheal tube (Portex) was introduced and ventilation assisted manually. HFJV was subsequently resumed by the tracheal route with an intermittent mandatory ventilation (IMV) system and there was no further extension of the surgical emphysema. A chest X ray demonstrated surgical emphysema in the neck with some mediastinal emphysema but no pneumothoraces.

The patient succumbed to bronchopneumonia and septicaemia 18 hours later and a postmortem examination was performed. Unfortunately, the minitracheotomy cannula had been removed but there was no evidence of false track and the surgical emphysema had resolved fully.

It was not possible to confirm the positioning of the resited cannula with total certainty but clinical signs of correct placement were unequivocal both before and after the acute episode. Assuming that cannula placement was correct, it is suggested that an increase in airway pressure resulted in a leak of gas around the minitracheotomy due to failure of the cricothyroid membrane to produce an airtight seal on re-insertion. The increase in airway pressure may have resulted from an episode of upper airway obstruction, possibly caused by laryngeal spasm, which prevented the inflowing gas from escape.

In summary, great caution is advocated upon commencement of HFJV through a minitracheotomy cannula even if the signs of correct placement are beyond doubt.

The Queen Elizabeth Hospital, D.N. STOKES
Birmingham B152TH

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2. FISCHER HBJ, SMITH BE. H.V.F. In: DELARUE NC, SCHAPASSE GE, eds. *International trends in general thoracic surgery, Vol. 2.* Eastbourne: W.B. Saunders, 1985.

Misplacement of a minitracheotomy tube

We report a complication of minitracheotomy. The patient was an 80-year-old woman who had undergone an oesophagogastrectomy following rupture of the oesophagus during dilatation of a benign oesophageal stricture. Postoperatively her lungs were ventilated electively for 3 days and she was extubated after 2 days of spontaneous ventilation through the tracheal tube. A Portex Minitrach II tube was inserted to aid physiotherapy and tracheal suction as described earlier.[1]

A soft suction catheter passed easily down the Minitrach and small amounts of blood were aspirated. However, no hiss of escaping gas could be heard over the end of the Minitrach tube during expiration. A chest radiograph showed the Minitrach tube to be lying in line with the trachea, which was deviated to the right. A small amount of radio-opaque contrast medium was injected down the tube and a subsequent radiograph showed passage of the contrast medium into the mediastinum. The tube could not be palpated in the neck and it was assumed that it had perforated the trachea laterally or posteriorly to enter the mediastinum. The trachea was re-intubated and the patient tolerated a tracheal tube for spontaneous ventilation for a further 3 days when she was extubated and made a slow but uneventful recovery.

We wish to make two points. Firstly, the absence of an audible hiss of escaping air over the end of a Minitrach tube almost certainly indicates blockage or misplacement. Secondly, placement of these tubes may be unpredictable in patients with tracheal deviation, as also suggested earlier.[1]

District General Hospital, Y. TRAN
Colchester CO4 5JL R. HEDLEY

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Speed of epidural injection

The article by Griffiths *et al.* (*Anaesthesia* 1987; **42:** 160) about speed of epidural injection confirms my own clinical impression that wider segmental spread occurs earlier with rapid injection. However, the suggestion that local anaesthetic be injected rapidly at a rate of about 1 ml/second is surely fraught with po-

tential dangers. The minimum dose of bupivacaine required to cause systemic toxicity when injected into an epidural vein (as opposed to a peripheral vein) is probably above 25 mg[1] but, in Crawford's recent review,[2] 10 ml 0.5% bupivacaine was enough to cause convulsions in two patients.

Peak blood concentrations of local anaesthetic are proportional to dose and inversely proportional to cardiac output and the time taken for injection. Therefore, shortening the injection time makes toxicity more likely.[3] Whether one believes in test doses or not, it is important to inject epidural solutions slowly and maintain rapport with the patient, as emphasised again recently by Wildsmith[4] and Prince and McGregor.[1] Only then will inadvertent intravascular or intrathecal injection become apparent before disaster strikes.

Leicester Royal Infirmary,
Leicester LE1 5WW

N.G. Lavies

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The pulse oximeter—an early warning device?

This letter describes the unexpected occurrence of a reduced oxygen saturation detected by a pulse oximeter during anaesthesia, the cause of which was not discovered until 35 minutes after the procedure.

A fit-looking, 75-year-old woman was admitted for resection of a large polyp of the vocal cords. She had been a heavy smoker until 3 years before, when she had a myocardial infarction. This was treated at home by her husband, a retired Community Physician. She was on digoxin 0.125 mg, had no angina and strenuously denied any breathlessness, even on exertion. Her ECG showed signs of a previous anterolateral infarct but with persistent elevation of the ST segment in leads V2 to V6. Her chest X ray showed cardiomegaly and a small left apical mass, probably in the posterior segment of the upper lobe. In view of the ECG, the radiologist was asked if he could exclude a ventricular aneurysm. Fluoroscopy was performed and reported as follows: 'The left ventricle is hypokinetic, but there is no obvious aneurysm.' He suggested that the small mass could be biopsied under X ray screening in the near future.

It was decided that surgery should be postponed until the lung biopsy had been performed. However, indirect laryngoscopy subsequently showed the vocal cord polyp to be more extensive than had been thought, and the surgeon had to reverse his decision.

Premedication was with glycopyrronium 0.2 mg. An intravenous cannula was placed in the left hand, a slow infusion of Hartmann's solution started, the ECG monitored and pre-oxygenation performed. Anaesthesia was induced with etomidate 100 mg and the trachea was intubated with a 5.0-mm Portex microlaryngeal tube using suxamethonium 100 mg. Her lungs were manually ventilated using a Bain system with nitrous oxide, oxygen and enflurane and intermittent suxamethonium to a total of 200 mg. The sessile, lobulated polyp, which arose from the full length of the left cord, was then resected.

When the pulse oximeter (Ohmeda Biox 3700) was attached to the patient's forefinger in theatre, the saturation was noted to be only between 87 and 92%. The position of the tube was checked and found to be correct. Increasing the inspired oxygen to 45% still only raised the saturation to 94%. The pulse rate was steady at 90–95 beats/minute and the blood pressure (Dinamap) varied between 150 and 190 mmHg systolic.

The trachea was extubated when the patient awoke and she was transferred to the recovery room on an MC oxygen mask, where her condition was satisfactory and no stridor was present. After 20 minutes the recovery staff requested that she be sent back to the ward but, in view of the extent of the polyp, it was decided to keep her in theatre under observation.

She was noted to be breathless about 15 minutes later. The anaesthetist was called and a clinical diagnosis of pulmonary oedema was made and confirmed on chest X ray. There was no laryngeal obstruction. She was treated with frusemide 40 mg and aminophylline 250 mg. After a prompt diuresis her condition gradually improved. She was transferred to the coronary care unit and given an isosorbide dinitrate infusion.

Later questioning disclosed that she had been on diuretics from her GP until 3 months before but her husband had decided that she did not need them and she had therefore stopped taking them. Recovery from her laryngeal surgery was uneventful and she was discharged home on diuretics 4 days later.

In retrospect, the low oxygen saturation recorded by the oximeter, should have warned of the impending pulmonary oedema. Frequently, pulmonary oedema does not show itself immediately in the recovery period, presumably because of peripheral vasodilatation. When the patient wakes fully and peripheral vasoconstriction occurs due to either pain or cold, fluid moves from the peripheral to the central circulation and clinical pulmonary oedema presents itself.

In our department, the value of this non-invasive monitor is increasingly appreciated. It would have been even more informative had it been attached in the anaesthetic room prior to induction, as is sometimes done with obviously ill patients. However, expensive machines are less prone to damage when kept in theatre on a permanent monitoring trolley.

With the limited equipment budget available, it is possible to increase the number of oximeters only gradually. Perhaps this case report supports an argument for having one, not only in every theatre, but also in every anaesthetic and recovery room.

Singleton Hospital,
Swansea SA2 8QA

R.A. Mason

Anaesthesia, 1987, Volume 42, pages 786–788

Book reviews

Evoked Potential Monitoring in the Operating Room

By M.R. Nuwer. Pp. ix + 246. Raven Press, 1986. US $40.00.

There is an agreeable tradition in newspapers in the weeks before Christmas when people are asked to choose their 'book of the year'. I would name Dr Nuwer's monograph on evoked potential monitoring and would urge you to look at it to see why.

This compact volume provides a resource compendium for anaesthetists, surgeons and neuroscientists who want to understand the basic principles and methodologies of this growing field. It is written by an experienced clinical neurophysiologist aware of the clinical benefits and the possible pitfalls of these complex but powerful techniques. He takes the view that a multidisciplinary team approach and proper equipment are required for their successful implementation.

Dr Nuwer's book is attractive because of his clear accounts of practicalities, his thorough critical reviews of the reports from groups using each technique and the plentiful illustrations of his and their results. There is a basic assumption, justified by the evidence presented, that evoked potential monitoring is an established method for increasing safety during a wide range of surgical procedures. Some realistic comments are made (in the context of spinal cord monitoring, but of wider relevance): 'In general the risk of damage to justify monitoring that nervous system pathway should be at least several percent. In addition it must be possible for the surgeon to alter the operating plan if the EP monitoring shows a possible impairment. If a surgeon has it in mind not to vary from the operating plan whether or not the monitoring shows damage, then there is no clinical reason for the monitoring to be undertaken.'

There is a strong emphasis on spinal cord and other somatosensory monitoring, perhaps reflecting the author's own interest as much as a judgement on the relative clinical utility of other evoked potential techniques. After a general introduction, the chapters include accounts of relevant basic electrophysiology, evoked potentials and signal processing, spinal cord monitoring, other somatosensory techniques, brainstem auditory monitoring and related techniques, visual system monitoring (somewhat cursory, but this is the least reliable intra-operative technique) and an account of basic studies including spinal tract lesions, spinal cord and brain ischaemia, mechanical injuries and techniques for electrical, but not magnetic, motor pathway stimulation. Physical factors, such as age, drugs, temperature and hypotension, that can affect the potentials, and also common technical factors that might lead to false results, are clearly and systematically detailed for each type of test. There is a pithy glossary of technical terms and an appendix that illustrates electrode placement conventions. The extensive list of references is relevant and admirably up to date and the index reliable.

It seems uncharitable to raise any point of criticism of such an excellent book but it is surprising to find that a few figures are either devoid of time base or calibration, or lack informative legends.

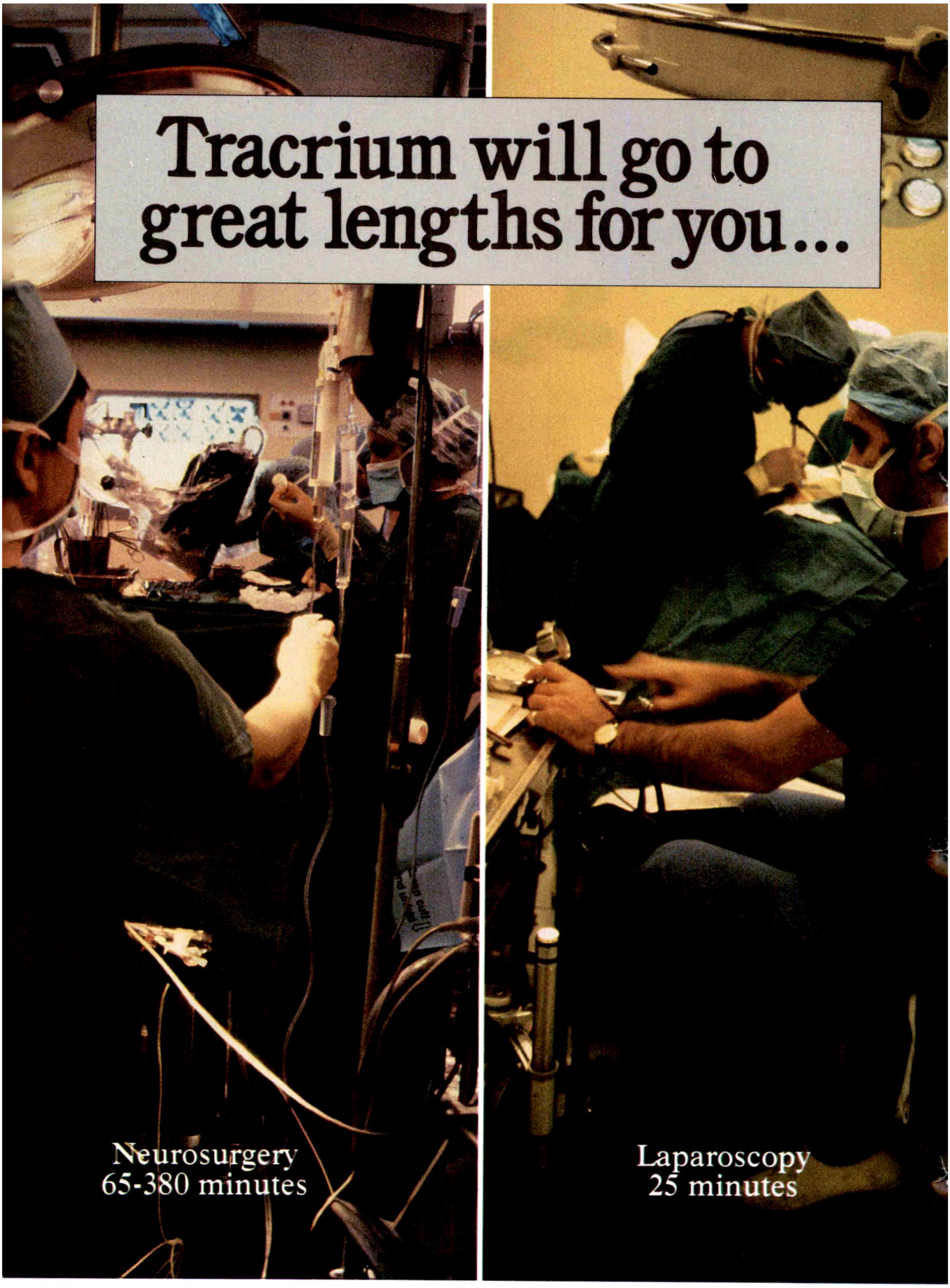
Dr Nuwer has considerable understanding of exactly how and why things go wrong during surgical operations that lead to postoperative neurological deficits. This makes the urgency for implementation of his recommended prophylactic monitoring techniques very evident. It is a matter for envy that he is able to assume the availability of adequate and appropriate staff and equipment in every hospital.

P.F. Prior

Anesthesia for Obstetrics, 2nd edition

Edited by S.M. Shnider and G. Levinson. Pp. xv + 566. Williams & Wilkins, 1987. £56.00.

This is the second edition of a well known American textbook under the editorship of Professor Shnider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and Dr Levinson, who also contribute to nine of the 39 chapters. The original text has undergone extensive revision and several new chapters have been added.

The first section deals with obstetric physiology and pharmacology, including perinatal pharmacology. The second contains six chapters on anaesthesia for vaginal delivery, and how nice it is to see an American text that differentiates between anaesthesia and analgesia in this respect and condemns the use of inhalational anaesthesia via a mask for delivery. The third section is the largest, with 10 chapters on obstetric complications, and of particular interest are those on anaesthesia for surgery during pregnancy, for fetal surgery and for pre-term labour. Section four deals with anaesthetic complications, including a chapter which would not immediately have sprung to the reviewer's mind, namely, obstetric anaesthesia and lawsuits; but it also deals with the problems of hypotension during regional anaesthesia, pulmonary aspiration and maternal mortality. Particularly welcome is section five, which concerns anaesthesia during pregnancy for a wide variety of non-obstetric disorders. Information has been scanty and scattered in this field and the editors are to be congratulated on commissioning these chapters which deal with the pregnant patient with cardiac disease, asthma, diabetes, neuromuscular disorders, morbid obesity, immunological disease and those about to undergo neurosurgery. The final section deals with the fetus and neonate in six chapters, and the book ends with an appendix, in tabular form, on the fetal and neonatal effects of maternally administered drugs.

Each subject is dealt with in depth. There are ample, clear illustrations and each chapter is heavily referenced. One is, however, puzzled as to why intraspinal opiates in obstetrics (which do not work anyway) should require 35% more space than regional anaesthesia for labour and delivery. One must also take issue with some points. Injection of a test dose of local anaesthetic through the needle rather than the catheter cannot be recommended. Neonatal depression following general anaesthesia is not related to the induction–delivery interval when aortocaval compression is avoided, but it is the uterine incision–delivery time that is important. One must also disagree with the modification of Sellick's manoeuvre illustrated in Figure 25.2. The method of application described by Sellick in 1961 has been shown to prevent regurgitated material from entering the pharynx with intragastric pressures up to 9.4 kPa. This method has not, and until it has, should not be used. There is also some repetition in the book, particularly with regard to antacid prophylaxis and management of hypotension. It should also be noted that dibucaine should appear under amide-linked agents, and not esters.

This is not a book for examination candidates, nor is it likely to be possessed by individual British anaesthetists, but as a reference work in the field it is unequalled.

M. Morgan

Emergency Anaesthesia

Edited by A.P. Adams, P.B. Hewitt and M.C. Rogers. Pp. 360. Edward Arnold, 1986. £12.75.

This is a pocket sized, well produced book which has as its target anaesthetists in training, those without ready access to a wide range of reference books and those who work in difficult situations or in developing countries. It is therefore aimed at a very wide audience and cannot please everyone. Experienced anaesthetists could no doubt argue with details in each chapter but this is not important when trying to provide a simple book on emergency anaesthesia. To satisfy such a wide variety of needs is difficult and there is a great danger of falling between stools. When there are 32 authors who all provide their own material the risks are even greater.

The editors have worked hard to draw together a wide spectrum of information but, with authors no doubt directing their contributions to different sections of the potential audience, the book is not easy to read as a whole. This is no great disadvantage since the reader is likely to be seeking information on a specific problem and will therefore turn straight to that section. Perhaps this is just as well because the order of the chapters is a little difficult to follow. It is, for example, surprising to find that the chapter on postoperative complications, which includes the only comments in the book on postoperative pain, appears right at the end of the book.

Some chapters, such as those on practical procedures, blood and intravenous fluids and on severe burns, are very well presented with a few excellent line drawings but more explanation on neuromuscular monitoring would have been helpful in the chapter devoted to monitoring, as would more detail on the techniques of commonly used local and regional techniques in that chapter. The review of local anaesthetic solutions is good.

Each chapter begins with a helpful list of topics to be covered and ends with a short, though remarkably comprehensive bibliography. In the chapter on developing countries most of the material is apposite although this is the first time I have seen bear mauling and camel bites specifically mentioned!

Will the book achieve its aim of being carried by junior anaesthetists? Its cost is modest, its size is similar to the BNF which is carried by young doctors, its presentation is robust and it certainly contains much useful information. I hope it will be a success since the aim is commendable but it may require some modifications in later editions to include more practical detail before it can be enthusiastically recommended.

W.R. MacRae

Problems in Obstetric Anaesthesia

Edited by B. Morgan. Pp. xi + 198. John Wiley, 1987. £32.50.

Problems in Obstetric Anaesthesia is the third volume in a series entitled *Perinatal Practice* which comprises topical reviews aimed at bridging the gap between obstetrics and neonatal medicine. This volume represents acknowledgment that the obstetric anaesthetist is an important member of the team involved in perinatal care and that problems in the anaesthetic care of obstetric patients are of interest to obstetricians, paediatricians and midwives as well as anaesthetists. A more positive impression could have been created if the title had emphasised the contribution of anaesthetists to the comfort and safety of the perinatal period, rather than the problems of anaesthesia.

The fourteen authors involved, ten anaesthetists, two physicians, a haematologist and an obstetrician, all work in well known UK hospitals but it is a pity that their qualifications, specialties and posts held are not specified. They all present interesting and helpful reviews of topics that range from subjects as broad as problems of general anaesthesia in obstetrics, to some as specific as disseminated intravascular coagulation. Inevitably some of the topics are so wide that only an outline of the problems can be covered, while others are dealt with in much greater detail.

There is an excellent review by Dr T. A. Thomas of complications of epidural anaesthesia which should prove very helpful in clarifying the role and management of this important part of current practice. The section on severe pre-eclampsia and eclampsia from the Cardiff authors and the contributions on the treatment of massive blood loss and shock in obstetric patients, provide useful guidance for establishing obstetric unit protocols for dealing with these emergencies.

A first rate review of amniotic fluid embolism from Dr M. Morgan brings his 1979 paper up to date. Problems of aspiration of gastric contents are well reviewed by Dr H. Seeley and the control of gastric acidity, problems of analgesia in labour and the fetal and neonatal effects of analgesic and anaesthetic drugs are all covered effectively.

In addition to a useful chapter on anaesthesia and maternal death by Dr D. Moir there are numerous references to the DHSS *Confidential Enquiries into Maternal Deaths* but it is a pity that the latest Report referred to is that of 1976–78, published in 1982, rather than the 1979–81 issue released in May 1986.

There are a number of misprints; the most important appears to be a recommendation for a dangerously high infusion rate for chlormethiazole. Otherwise the standard of the reviews is excellent; all are interesting, some are very basic and practical, others more abstruse and less conclusive. Some have extensive references, others have very selective lists. Overall this is a useful presentation of the current state of British obstetric anaesthetic practice with discussion of problems still to be overcome.

This book should be read by all those interested in improving perinatal care whether they are anaesthetists or members of the other specialties involved. For the trainee it is relatively expensive compared with standard UK obstetric anaesthesia texts but should be well used when purchased for departmental libraries.

P.B. Hewitt

Anaesthesia, 1987, Volume 42, pages 789–794

Anaesthetic literature

This section of *Anaesthetic literature* contains references taken from *Current Contents—Life Sciences* for February 1987. The Journals which may be consulted when *Anaesthetic literature* is compiled are those listed in *Current Contents—Life Sciences*, published by the Institute of Scientific Information, Philadelphia, Pennsylvania, USA.

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The collator of this section is Dr L. Kaufman, MD, FFARCS, Anaesthetic Office, The Rayne Institute, University College, University Street, London WC1E 6JJ. Dr Kaufman is prepared to provide on request, and at a modest charge, a new additional service to our readers. References from January 1984 have been entered on data base. The data are held on Dbase II, cpm 86 and on Dbase III, MsDos and are available on disc, together with a program providing search facilities. Enquiries direct to Dr Kaufman at the above address please.

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Treatment and medication

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Physiology

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Treatment and medication

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Treatment of respiratory failure during sleep in patients with neuromuscular disease—positive-pressure ventilation through a nose mask. ELLIS, E.R., BYE, P.T.P. *et al. American Review of Respiratory Disease* 1987; **135:** 148.

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Physiology

Effects of hyperventilation on pattern-reversal visual evoked potentials in patients with demyelination.

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Treatment and medication

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Endocrine and metabolic

Physiology

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Effects of alpha-1 adrenergic blockade on the hormonal response to hypoglycaemic stress in normal man. CUNEO, R.C., LIVESEY, J.H. *et al. Clinical Endocrinology* 1987; **26:** 1.

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The renin–angiotensin–aldosterone system in normal 85-year-old people. SKOTT, P., INGERSLEV, J. *et al. Scandinavian Journal of Clinical and Laboratory Investigation* 1987; **47:** 69.

Altered liver function in diabetes—model experiments with aminopyrine in the rat. ZYSSET, T., TLACH, C. *Journal of Pharmacology and Experimental Therapeutics* 1987; **240:** 271.

Treatment and medication

Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. BAYLISS, J., NORELL, M. *et al. British Heart Journal* 1987; **57:** 17.

Diuretic-induced hypokalemia and altered renal function. CARNEY, S.L., MORGAN, T.O. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1986; **24:** 665.

Increase in insulin antibodies during continuous subcutaneous insulin infusion and multiple-injection therapy in contrast to conventional treatment. DAHL-JORGENSEN, K., TORJESEN, P. *et al. Diabetes* 1987; **36:** 1.

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Altered furosemide pharmacokinetics in chronic alcoholic liver disease with ascites contributes to diuretic resistance. PINZANI, M., DASKALOPOULOS, G. *et al. Gastroenterology* 1987; **92:** 294.

Relationship between transcutaneous oxygen tension, ankle blood pressure, and clinical outcome of vascular surgery in diabetic and nondiabetic patients. WYSS, C.R., ROBERTSON, C. *et al. Surgery* 1987; **101:** 56.

Pain

Physiology

Activation of inhibition from the periaqueductal grey matter mediates central analgesic effect of metamizol (dipyrone). KARLSSON, K.H., HELMREICH, J., JURNAL, I. *Pain* 1986; **27:** 373.

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Other

Treatment and medication

The management of nausea and vomiting in clinical oncology. CRAIG, J.B., POWELL, B.L. *American Journal of the Medical Sciences* 1987; **293:** 34.

Anaesthesia, 1987, Volume 42, pages 795–796

Obituaries

Knight, Ronald Frank, MB, BS, FFARCS, DA, DTM & H, formerly Consultant Anaesthetist at Wycombe General Hospital. Qualified from Charing Cross Medical School in 1956.
Roper, Richard Edward, MB, ChB, FFARCS, formerly Consultant Anaesthetist at Whiston Hospital. Qualified from the University of Liverpool in 1968.
Todd, Christopher Granville, MB, BCH, FFARCS, formerly Consultant Anaesthetist at Craigavon Area Hospital. Qualified from the Queen's University, Belfast in 1982.

International congress calendar

1987

20–23 July. London. *Second International Symposium on the History of Anaesthesia.*
Information: Secretariat of the Second International Symposium on the History of Anaesthesia, Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA.

2–7 August. Hamburg. *Vth World Congress on Pain.*
Information: Hamburg Messe & Congress, Postfach 30 24 80, 2000 Hamburg 36, Federal Republic of Germany.

4–8 August. Quality Inn, Nelson. *Conference of Anaesthetists of New Zealand Annual Meeting.*
Information: Dr M. L. Farrant, Secretary CANZ 87, Nelson Hospital, Private Bag, Nelson, New Zealand.

23–28 August. Sydney, Australia. *10th International Congress of Pharmacology.*
Information: The Secretariat, 10th IUPHAR Congress, GPO Box 2609, Sydney, NSW 2001, Australia.

26–28 August. Edinburgh. *Edinburgh Anaesthesia Festival.*
Information: The Department of Anaesthetists, Royal Infirmary, Edinburgh EH3 9YW, UK.

27–30 August. Kobe, Japan. *International Symposium on Cardiovascular Anesthesiology and 8th Annual Meeting of Japan Society of Circulation Control in Medicine.*
Information: Secretariat, ISCVA/SCC, Japan Convention Services, Inc., Kansai Branch, Sumitomo Seimei Midosujui Building, 1 DF 4-14-3, Nishitemma, Kita-ku, Osaka 530, Japan.

2–5 September. Singapore. *Fifth Association of South East Asian Nations Congress of Anaesthesiologists.*
Information: Congress Secretariat, 5th ASEAN Congress of Anaesthesiologists, World Express PTE Ltd, 114 Middle Road, 05-01 Singapore 0718.

3–6 September. Ghent, Belgium. *European Academy of Anaesthesiology 9th Annual Meeting.*
Information: Professor Dr G. Rolly, Department of Anaesthesiology, Academic Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.

10–11 September. Sheffield. *Annual Scientific Meeting, Association of Anaesthetists of Great Britain and Ireland.*
Information: The Honorary Secretary, The Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA.

15–18 September. Paris, France. *IIIrd International Symposium on Pediatric, Surgical and Neonatal Intensive Care.*
Information: SOCFI, 14 Rue Mandar, 75002 Paris, France.

26–30 September. Alice Springs, Australia. *Australian Society of Anaesthetists Annual General Meeting.*
Information: ASA, PO Box 600, Edgecliff, NSW 2027, Australia.

10–14 October. Atlanta, Illinois. *Annual Meeting, American Society of Anesthesiologists.*
Information: John Andes, Esq., 515 Busse Highway, Park Ridge, IL. 60068, USA.

16–18 October. Toronto, Canada. *Paediatric Anaesthesia Conference.*
Information: Paediatric Anaesthesia Conference, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

22–24 October. Posnan, Poland. *Symposium—DYDAKTYKA '87.*
Information: The Organising Committee of Symposium DYDAKTYKA '87, Institute of Anaes-

thesiology and Intensive Therapy, ul. Przybyszewskiego 49, 60-355 Poznan, Poland.

22–24 October. Berlin. *2nd International Steglitz Symposium.*
Information: Priv.-Doz. Dr K. Reinhart, Klinikum Steglitz, Freie Universität Berlin, Hindenburgdamm 30, 1000 Berlin 45, Federal Republic of Germany.

4–5 November. Baltimore, Maryland. *Progress in in vitro Toxicology.*
Information: Jeanne Ryan, Program Coordinator, Office of Continuing Education, The Johns Hopkins Medical Institutions, 720 Rutland Avenue, Baltimore, MD 21205, USA.

5–7 November. Oporto, Portugal. *International Meeting on Anaesthesia and Intensive Care.*
Information: Anaesthesia Department, Hospital S. Joao, Oporto, Portugal.

7–8 November. New York. *Bernard H. Eliasberg Memorial Symposium: The Cardiac Patient for Non-Cardiac Surgery—The Experts Opine.*
Information: Department of Anesthesiology, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York 10029, USA.

8–13 November. *IIIrd Panamerican and Iberic Congress on Intensive and Critical Care Medicine.*
Information: Sociedad Venezeolana de Medicina Critica, Colegio Medico del Edo. Miranda, Calle Ele Golf, Quinta La Setenta y Seis, Caracas, Venezuela (PO Box 68.625, Altamira, Caracas 1062).

11–16 November. Guangzhou, People's Republic of China. *Anaesthesia China '87.*
Information: Anaesthesia China '87, International Conference Consultants Ltd, 1st Floor, 57 Wyndham Street Central, Hong Kong.

14–15 November. Rotterdam, The Netherlands. *International Symposium on Surfactant Replacement Therapy.*
Information: Dr B. Lachmann, Department of Anesthesiology, Erasmus University, Postbox 1738, 3000 DR Rotterdam, The Netherlands.

16–20 November. Rotterdam, The Netherlands. *The 4th International Symposium on Applied Physiology in Cardio Respiratory Emergencies.*
Information: Omar Prakash, MD, Erasmus University, Postbox 1738, 3000 DR Rotterdam, The Netherlands.

13–17 December. New York. *40th Postgraduate Assembly in Anesthesiology.*
Information: Mr Kurt G. Becker, Executive Director, The New York State Society of Anesthesiologists, Inc., 30 East 42nd Street, Suite 1501, New York 10017, USA.

1988

11–13 May. Sydney, Australia. *5th International Dental Congress on Modern Pain Control.*
Information: Australian Convention and Travel Services (ACTS), GPO Box 1929, Canberra, ACT 2601, Australia.

22–28 May. Washington, DC. *9th World Congress of Anesthesiology.*
Information: American Society of Anesthesiologists, 515 Busse Highway, Park Ridge, IL 60068, USA.

15–16 September. Southampton. *Annual Scientific Meeting, Association of Anaesthetists of Great Britain and Ireland.*
Information: The Honorary Secretary, The Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA.

1 October. Pavia. *National Congress, Societa Italiana di Anest, Rianimazione e Terapia Intensiva.*
Information: Dr G. Conti, SIARRTI, Universita degli Studi, La Sapienza di Roma, Viale del Policlinico, 00161 Roma, Italy.

29 October–2 November. Ballarat, Victoria. *Annual General Meeting, Australian Society of Anaesthetists.*
Information: The Secretariat, ASA, PO Box 600, Edgecliff, NSW 2027, Australia.

1989

12–16 August. Christchurch, New Zealand. *Combined Meeting, New Zealand Society of Anaesthetists and Australian Society of Anaesthetists.*
Information: ASA, PO Box 600, Edgecliff, NSW 2027, Australia.

3–8 September. Kyoto, Japan. *Fifth World Congress on Intensive and Critical Care Medicine.*
Information: The Fifth World Congress on Intensive and Critical Care Medicine, c/o Japan Convention Services, Inc., Nippon Press Center Building, 2-2-1 Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan.

1990

9–15 September. Warsaw. *VIIIth European Congress of Anaesthesiologists.*
Information: The Organising Committee, VIIIth European Congress of Anaesthesiologists, c/o Polish Society of Anaesthesiology and Intensive Therapy, ul. Kasprzaka 17a, 01-211 Warsaw, Poland.

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Safety Information Bulletin

These are issued regularly by the Department of Health and Social Security

Penlon off-line hoses. SIB(87)17

Some of these hoses have fractured near to the vaporizer connexions. Replacement hose assemblies are available from the manufacturers. Pre-use check on the tightness of these connectors is recommended. All off-line hoses should be replaced every 2 years. New connector clips are available from Penlon Limited.

Chemetron humidifier: Model MICH Humidity Centre. SIB(87)19

A serious scald has resulted from overheating of this device since there is no independent over-temperature safety cut-out as is required by BS5724. These devices should not be used unless there is an independent over-temperature cut-out device.

Oxygen/air mixers. SIB(87)26

A previous hazard warning (HN(81)4) about the influx of air into the oxygen piped medical gas supply system has now been followed by the design of an improved non-return valve for use with Mediada gas mixers. It is still recommended that these mixers are disconnected from the gas source when they are not in use and that they are not coupled to a 700 kPa air supply. They are designed to work off a 400 kPa supply. These mixers should be serviced regularly.

Syringes: correct use with syringe pumps. SIB(87)27

It is essential that the make of syringe is matched with the appropriate syringe pump before these are used. If this advice is not followed there may be an error in infusion rate of up to 20%.

Enquires about all the above may be made to the appropriate person as specified below.

England
Mr L.F.G. Small or Mr R. Glover,
DHSS,
NHS Procurement Directorate,
14 Russell Square,
London WC1B 5EP
(Tel: 01 636 6811 Ext. 3045/3371)
Quoting DEF/24/3/8

Wales
Welsh Office,
Health Services Planning Division,
Cathays Park,
Cardiff CF1 3NQ
(Tel: 0222 023647)

Scotland
Scottish Health Service,
CSA, Supplies Division,
Scientific and Technical Branch,
Trinity Park House,
South Trinity Road,
Edinburgh EH5 3SH
(Tel: 031 552 6255 Ext. 2478)

N. Ireland
Chief Engineer's Branch,
Department of Health and Social Services,
Central Works Unit,
Stoney Road,
Dundonald,
Belfast BT16 0US
(Tel: 02318 4535 Ext. 28)

Hazard notice

Siemens Servo Ventilator, 900 Series (900, 900B, 900C and 9000). HN(87)1

Silicone rubber expiratory valves in these ventilators need to be cleaned regularly and replaced after every 1000 hours' use. There have been a number of complaints that the valves have split prematurely across the axis of the valve after very brief usage. This is normally recognised by the internal monitoring and alarm system but a potential for serious harm exists.

Vickers' Syringe Drive Pumps SP 44, SP 55. HN(87)2

Several reports have been made that these pumps have discharged the contents of the syringe too rapidly. No explanation for this failure has yet been demonstrated. Extra vigilance in the use of these pumps is recommended.

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Manuscripts will be reviewed for possible publication on the understanding that they are being submitted to one journal at a time and have not been published, simultaneously submitted, or already accepted for publication elsewhere. This does not preclude consideration of a manuscript that has been rejected by another journal or of a complete report that follows publication of preliminary findings elsewhere, usually in the form of an abstract. Investigations performed on man must conform to appropriate ethical standards including voluntary, informed consent and acceptance by an ethical committee. Articles accepted become copyright of *Anaesthesia*.

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Dr J. N. Lunn, Editor of ***Anaesthesia****, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, UK.*

PREPARATION OF MANUSCRIPTS

Articles for *Anaesthesia* should be prepared in accordance with *Uniform requirements for manuscripts submitted to biomedical journals* (*British Medical Journal* 1979; 1: 532–5) except that the titles of journals in the reference section should be given in full (see below). A reprint of these requirements of which this notice is a summary, can be obtained from the *British Medical Journal* price 50 pence (UK).

Type manuscripts on white bond paper, 20.3 × 26.7 cm or 21.6 × 27.9 cm (8 × 10½ in. or 8½ × 11 in.) or ISO A4 (212 × 297 mm) with margins of at least 2.5 cm (1 in.). Use double, and preferably triple, spacing throughout, including the references. Please do not use a dot matrix printer, particularly one with poor quality descenders or ascenders. Unseparated, fan-folded manuscripts may be returned to the author. *The manuscript* should consist of the following sections in this order each beginning on a new page: *title page*, *summary* and *key words*, *text*, *acknowledgments*, *references*, *individual tables*, and *legends for figures*.

Number pages consecutively, beginning with the title page.

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The name of the author and the address to which proofs and other correspondence are to be addressed should appear in the top left-hand corner of the sheet.

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Start a new sheet

The second page should carry a summary of not more than 150 words. The summary should state the purpose of the study or investigation, basic procedures, main findings and their statistical significance, and the principal conclusions.

Do not use abbreviations except for units of measurement (e.g. mg, cm, etc.).

Key (indexing) words. Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers. Use terms from the Medical Subject Headings list from *Index Medicus*. The Editor may modify these at proof stage to conform with agreed practice of certain other anaesthetic journals in the English language.

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(*continued overleaf*)

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The text of observational and experimental articles, case reports, etc. is usually divided into sections with the headings *Introduction*, *Methods*, *Results* and *Discussion*. Long articles will need subheadings within some sections to clarify their content.

Letters for the correspondence pages should be double spaced and prepared in accordance with the format in a recent copy of *Anaesthesia*.

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Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by arabic numerals. References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration. Use double or treble spaced typing.

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Corporate author

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. *Scandinavian Journal of Clinical Laboratory Investigation* 1976; **36:** 119–25.

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BOOKS AND OTHER MONOGRAPHS

Personal author(s)

OSLER AG. *Complement: mechanisms and functions.* New York: Prentice-Hall, 1976.

Corporate authors

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Chapter in book

WEINSTEIN L, SWARTZ MN. Pathogenic properties of invading micro-organisms. In: SODEMAN WA Jr, SODEMAN WA, eds. *Pathologic physiology: mechanisms of disease.* Philadelphia: W.B. Saunders, 1974: 457–72.

Agency publication

National Center for Health Statistics. Acute conditions: incidence and associated disability, United States, July 1968—June 1969. Rockville, MD: National Center for Health Statistics, 1972. (*Vital and health statistics, Series* **10:** Data from the National Health Survey, No. 69) [DHEW publication No. (HSM) 72–1036].

OTHER ARTICLES

Newspaper article

SHAFFER RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help to cure alcoholism and insomnia, explain mental illness. How the messengers work. *Wall Street Journal* 1977 Aug 12: 1(col 1), 10(col 1).

Magazine article

ROUECHE B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971 Sept 4: 66–81.

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REVIEW JOURNALS

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Anesthesiology

E. Freye

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1987. IX, 108 pages. Soft cover DM 52,–.
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Volume 176

H. J. Wüst, M. D'Arcy Stanton-Hicks (Eds.)

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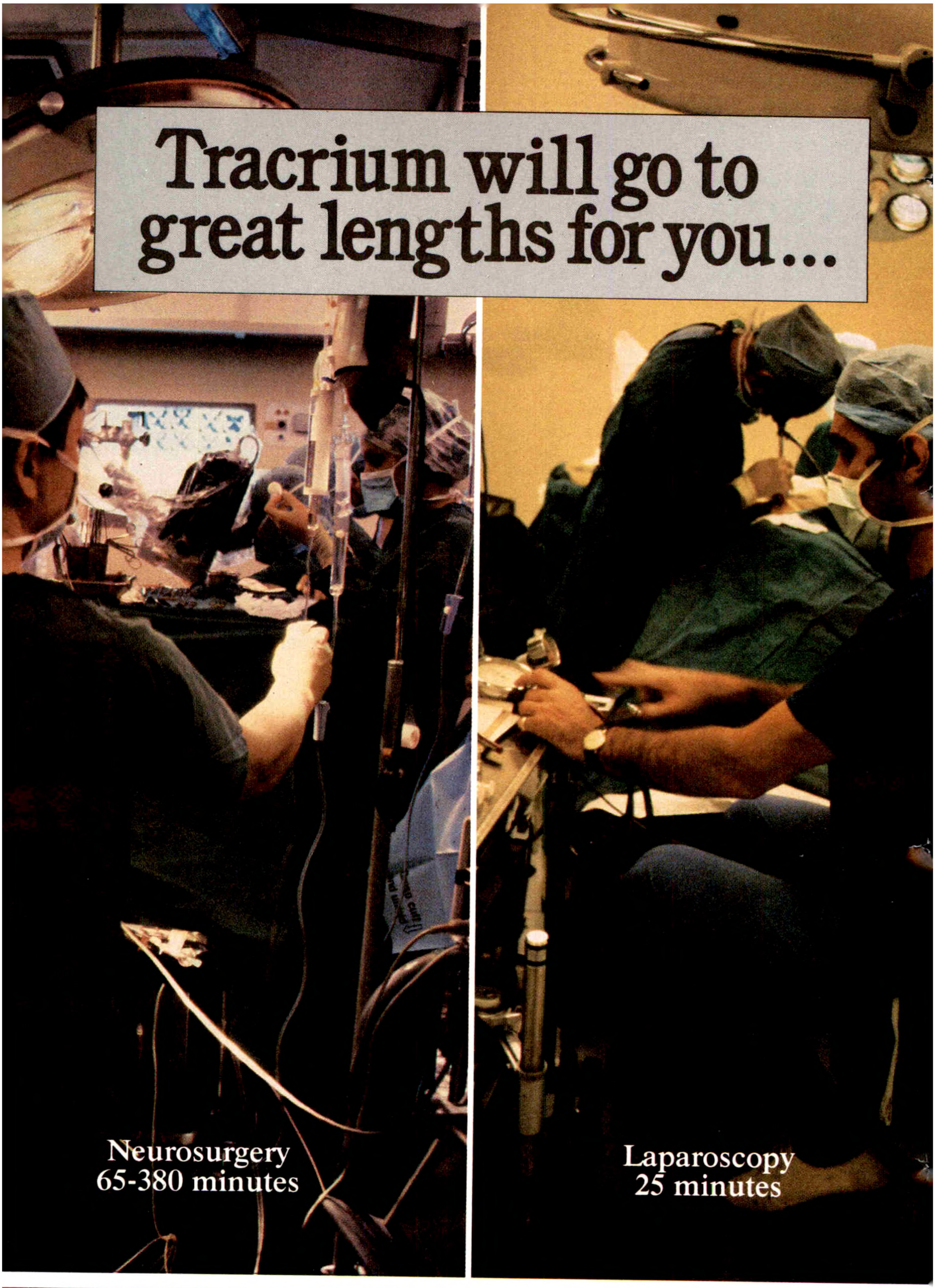
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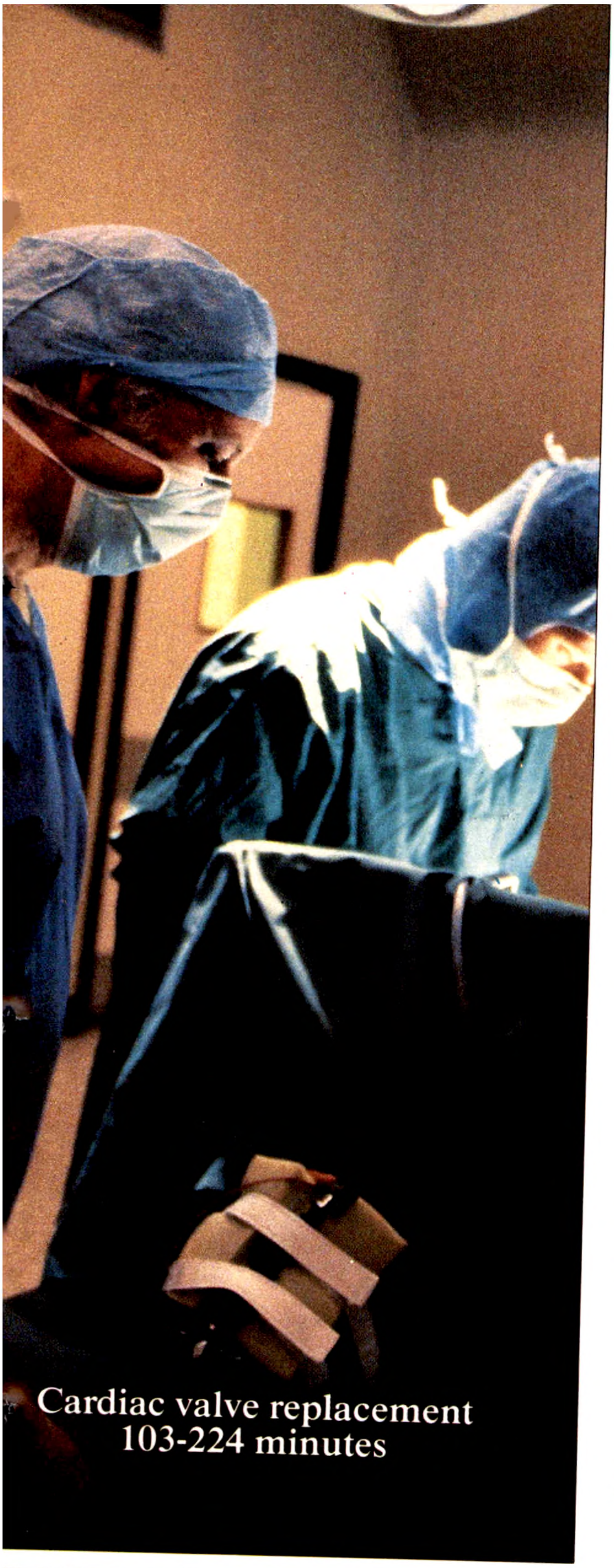

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Anaesthesia, 1987, Volume 42, pages 799–800

Editorial

Zidovudine and the anaesthetist

The recent introduction of zidovudine (Retrovir), 3′-azido-3′-deoxythymidine (AZT), for the treatment of acquired immunodeficiency syndrome (AIDS) may carry implications for the anaesthetist who looks after these patients, in addition to those presented by the disease itself.[1–3] AZT is a dideoxynucleoside which, when successively phosphorylated in the host cell to its triphosphate, acts as a false substrate for the enzyme reverse transcriptase. Human immunodeficiency virus (HIV), a retrovirus, uses reverse transcriptase to produce a deoxyribonucleic acid (DNA) copy of itself for incorporation into the host cell genome. When AZT-5′-triphosphate is incorporated into the DNA sequence the azido substitution makes further $5' \rightarrow 3'$ phosphodiester linkages impossible and, therefore, DNA chain synthesis is terminated. Host cell DNA polymerases are also inhibited but to a much lesser extent. It also depletes cellular pools of thymidine triphosphate and other pyrimidine bases (the natural substrates for viral and host DNA polymerases) by inhibition of the enzyme thymidylate kinase.[4]

Adverse effects seen during therapy so far, have been mainly haematological and neurological. Host cell DNA polymerase inhibition in the bone marrow affects primarily white and red cell precursors and leads to anaemia and neutropaenia in most patients who receive high doses of oral AZT (90 mg/kg per 24 hours) for 4–6 weeks, and in some subjects who have lower doses (25–30 mg/kg per 24 hours) for more than 8 weeks. However, in such cases a lower dose can usually be tolerated subsequently.[5,6] Platelet production does not appear to be significantly depressed. The anaemia is of the megaloblastic type and is more severe in the presence of pre-existing bone marrow depression, for example, from vitamin B_{12} and folate deficiency. In view of the current interest in nitrous oxide as it affects folate metabolism, the possibility of a nitrous oxide–AZT interaction should be considered since they both result in reduced availability of thymidine-5′-triphosphate for DNA synthesis. In any case, the normal precautions before anaesthesia in anaemic patients would apply. Neurological symptoms secondary to treatment may be confused with the development of neurological complications of the disease and the anaesthetist should be aware that neurological deterioration after regional or general anaesthesia might be attributed to the anaesthetic technique. Proper evaluation and documentation of pre-existing neurological signs and symptoms are an important part of the preoperative assessment of these patients.

AZT is administered orally or intravenously at intervals of 4–8 hours; a single dose of 5 mg/kg orally or 2.5 mg/kg intravenously results in a peak serum concentration of approximately 5 μmol/litre. Total daily dosage is in the range 15–60 mg/kg. Protein binding is fairly low (34–38%) and plasma half-life is about one hour. The drug achieves good penetration to the cerebrospinal fluid and it may appear in the breast milk. AZT is metabolised in the liver and is actively secreted to the renal tubules. Pharmacokinetic interactions might therefore be anticipated with drugs which share these mechanisms as their major routes of inactivation and excretion. For example, the pharmacological effects of aspirin, morphine, codeine and paracetamol may be enhanced by competition with AZT for glucuronic acid conjugation. Similarly, concurrent treatment with these drugs may increase the incidence of undesirable side effects from AZT. No adverse effects on cardiac, renal or hepatic function have so far been noted that could not have been attributable to the disease itself in AIDS patients.

It is important that data be collected in order to determine the incidence of significant drug interactions with AZT during anaesthesia. This department of anaesthesia is willing to collate, for further publication, information from anyone who has anaesthetised a patient receiving treatment with AZT, whether or not any unexpected reaction or event ensued.

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A.J. Phillips
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Editorial notices

Anaesthesia News

Copy for *Anaesthesia News* should be sent to the Editor as and when it becomes available. It is hoped that publication will occur within 3 months of receipt.

Submission of manuscripts

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Anaesthesia, 1987, Volume 42, pages 801–807

Tactile orotracheal tube placement test

A bimanual tactile examination of the positioned orotracheal tube to confirm laryngeal placement

P. CHARTERS AND K. WILKINSON

Summary

The development of a tactile clinical test of the positioned orotracheal tube is described which allows confirmation of its location within the larynx. It was possible, after preliminary experience with the test, to confirm laryngeal placement confidently in an average of 97% of cases in two concurrent series each of which consisted of 100 patients. Inevitably, there are limitations to its usefulness but it has the advantage that no special apparatus is required for its performance. The implications of this test are discussed in relation to difficult intubation, obstetric anaesthesia, the teaching of applied anatomy and checking by their trainers of intubations performed by very junior anaesthetists. Familiarity with this test should be considered essential for its reliable implementation.

Key words

Intubation, orotracheal.

Howells[1] reported in 1985 that he had abandoned pre-oxygenation prior to tracheal intubation and claimed that this would only increase the risk of delayed recognition of oesophageal misplacement of the tube. There has been a relatively muted response in the anaesthetic literature to such a challenging statement. The statement appears to be constructed around two fundamental problems which are closely related. Under certain circumstances, even senior anaesthetists have been misled into believing that the tracheal tube was correctly placed when this was not the case.[2–6] However, apart from direct visualisation of the tracheal tube as it passes between the vocal cords, most of the other clinical tests to confirm tracheal placement have been shown to be fallible.[2–9]

These clinical tests have received little objective scrutiny to determine their reliability, or the circumstances under which their usefulness should be questioned. Latto[9] recently graded the tests as reliable, probably reliable or unreliable, but he offered no new evidence in support of this grading; it is presumably based on the grounds of documented case reports and general clinical impression. Even cyanosis has been shown to be fallible.[2]

Bearing in mind this uncertainty about the current tests, an approach to the problem was made by trying to develop a test to confirm laryngeal intubation based on the sense of touch. A pilot study was undertaken with a preliminary idea of the form which the test should take, in which 50 consecutive patients were examined after normal tracheal intubation. This resulted in an 82% success rate. As evolutionary changes were still made to the test during the pilot study, and since it was clear that experience with the

P. Charters, MD, MRCP, FFARCS, Consultant, Clatterbridge Hospital, Bebington, Wirral L63 4JY, K. Wilkinson, MB, ChB, MRCP, Registrar, Arrowe Park Hospital, Upton, Wirral L49 5PE.

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techniques was required for success, it was felt that a larger study was warranted.

Method

Tactile orotracheal placement test (TOP test)

Prior to formal description of the test, which consists of two parts, some preliminary notes are necessary. It is assumed that the orotracheal tube has been passed but not tied in, as this allows greater mobility of the structures to be examined. The hand which is to enter the patient's mouth, is protected by a thin, disposable, polythene glove. Prior inspection should have alerted the examiner to any loose or sharp teeth. The optimum height for the patient's head is just below the level of the examiner's umbilicus. The test is facilitated by a slightly exaggerated extension of the head on the neck. The tests are described as for a right-handed examiner who stands to the patient's left side alongside the head and shoulders.

Test 1 (side test)

The examiner opens the mouth and directs the index finger of the right hand into the left side of the patient's mouth (Fig. 1). With the index finger kept as far into the angle of the mouth as

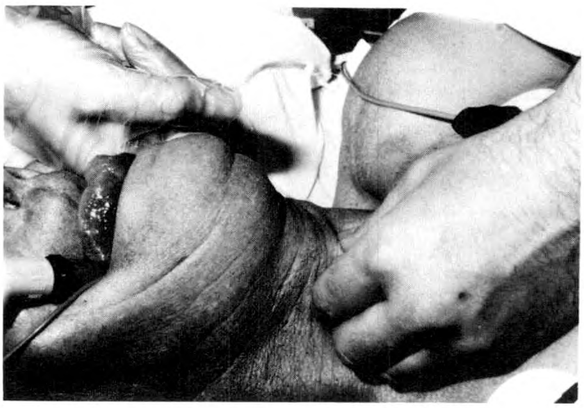

Fig. 1. TOP test 1: insertion of the examiner's right index finger into the corner of the left side of the mouth down to the level of the left arytenoid. The tracheal tube is not tied in because this allows greater mobility of the structures for the next stage of the test. Note that the tongue is well forward.

Fig. 2. TOP test 1: the examiner's left hand is now located at the lower part of the larynx to rotate it upwards in an anti-clockwise direction and so present the interarytenoid groove to the examiner's right index finger.

possible, it is then advanced down the side of the pharynx; care is taken not to trap the patient's lip in so doing. The first structure to be negotiated is the hyoid, which is an obvious bar that traverses the line taken by the finger (its identity can be confirmed by taking the hyoid in the finger and thumb of the left hand on the outside of the patient's neck and moving it about). Palpation in a forward direction along the hyoid reveals the lateral border of the epiglottis and, moving downwards again along-side this, the left arytenoid is palpable.

The tracheal tube should now have been felt medial to the arytenoid. With the right index finger kept on the left arytenoid, the lower part of the larynx is taken in the examiner's left hand at the front of the patient's neck. The right index finger is rotated backwards along the surface of the arytenoid, while the left hand is used to rotate the larynx anticlockwise up towards the right hand (Fig. 2), coordinating the movements of both hands. As it continues along the left arytenoid, the right index finger first drops into the interarytenoid groove and then comes on to the right arytenoid (Fig. 3). A positive test is defined as a location of the tracheal

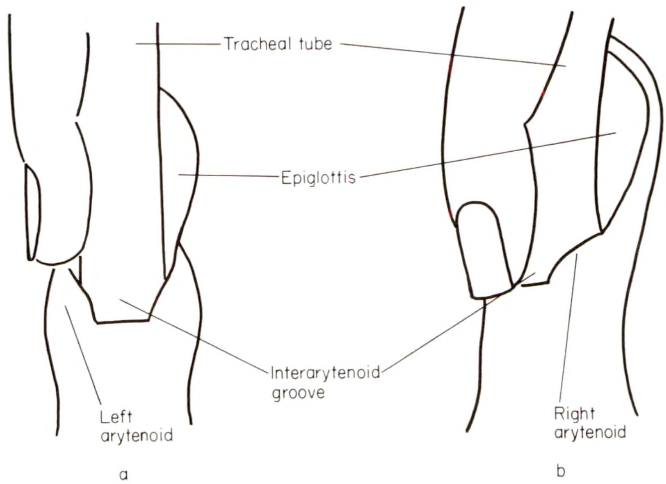

Fig. 3. TOP test 1: negotiation of the interarytenoid groove by the examiner's right index finger: (a) view of the larynx from behind, showing the tip of the finger in position on the left arytenoid; (b) the larynx rotated and moved upwards, with the finger tip moving round into the interarytenoid groove. In both diagrams the width of the lower part of the groove is exaggerated for the sake of clarity.

Fig. 4. TOP test 2: the examiner's right hand is just entering the mouth. Note that the ring and little fingers remain outside the mouth, in line with the examining index and middle fingers.

tube immediately anterior to the interarytenoid groove. Delineation of the boundaries of the groove by the index finger, ensures its certain identification.

Test 2 (central test)

The second test, as an alternative and complementary to the first, again depends on establishing the relationship of the tracheal tube to the interarytenoid groove, but examination is via the surface of the tube itself. Firstly, the mouth is opened as widely as possible with the head fully extended on the neck. In addition, a rotation of about 10° (about a longitudinal axis) of the head towards the examiner seems to help in larger male patients. The index and middle fingers of the right hand are then inserted into the mouth over the top of the tracheal tube (Fig. 4). The ring and little fingers should stay outside the mouth in line with the examining fingers. A little forward movement of the tube is particularly helpful as the index and middle fingers of the right hand are advanced along and behind the tracheal tube.

If it is not possible to identify the interarytenoid groove merely by advancing the examining fingers, then the left hand is used to move the larynx in a rostral direction, again with a slight anticlockwise rotation (Fig. 5). This enables the tip of the right middle finger (as opposed to the index finger in the first test) to discover the interarytenoid groove and delineate its boundaries.

Patients

Each of the authors examined 100 consecutive patients who required tracheal intubation. In one series (series A) obstetric and gynaecological patients predominated, while the other (series B) comprised mainly patients undergoing general surgery. Any clinical features that suggested the possibility of difficult intubation were noted when the patients were seen preoperatively. Dentition was examined to record the presence or otherwise of the left lower molar teeth, as the pilot study had indicated that ease of performance of the tactile tests would be influenced by this. Width of mouth opening was also determined. The view of the vocal cords at laryngoscopy was graded 1 to 4 as defined by Cormack and Lehane.[10]

TOP tests 1 and 2 were performed following intubation. In addition, the following measurements were made in order to define the variability in anatomy: from the left corner of the mouth to the hyoid; from the hyoid to the arytenoid; from the upper incisors or gums to the epiglottis; and the width of the interarytenoid groove. Postoperative assessment was made on the day following operation in series B and consisted of a symptomatic enquiry.

Results

Table 1 indicates the age and sex differences for the two groups and also records the results of the TOP tests. The probability of success for

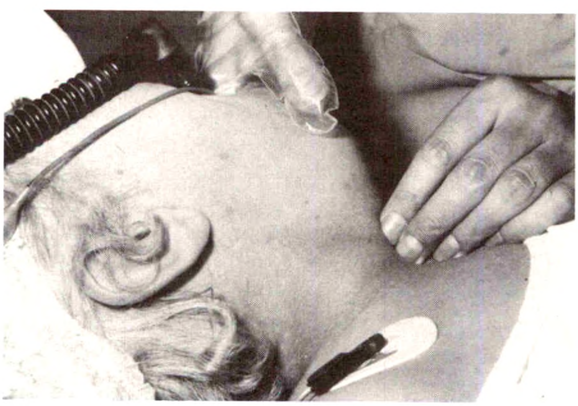

Fig. 5. TOP test 2: the right middle finger is approaching the interarytenoid groove. Note the extension of the head on the neck and slight rotation of the head towards the examiner.

Table 1. Test scores.

	Series A	Series B
Males/females, %	17/83	65/35
Mean age (SD), years	38 (17)	62 (16)
Both tests positive	74%	65%
Test 1 only, positive	22%	25%
Test 2 only, positive	2%	6%
Neither test positive	2%	4%

each test was comparable between the two series, despite the obvious age and sex differences between them.

The tests were generally easier in women and more difficult when 'dental block' was present (the definition of dental block used in this connexion, was the presence of any or all of the lower left molar teeth). This is reflected in the relative success rates shown in Table 2. Ninety-seven per cent of the 107 patients with dental block had 16 or more teeth (half the normal maximum); only 14% of the remaining patients were so well endowed.

None of the patients in either of the series was deemed to present a difficult intubation. In series A, all of the patients were grade 1 at laryngoscopy (i.e. most of the glottis seen) while in series B, only two patients were grade 2 (arytenoids only seen) and the rest were grade 1. Of the two patients graded 2, one had neither of the TOP tests positive.

Table 3 shows the mean, standard deviation and range of the distances measured. The four patients with the greatest limitation of mouth opening (25 mm) all had at least one positive TOP test. Morphological features, in terms of underlying structures within the arytenoids, were not usually detected. A vertical bar was noted in seven patients and in two, a triangular plate was evident.

Postoperative assessment revealed, in particular, that neither hoarseness nor sore throat was an important symptomatic problem.

There were no difficult intubations in the series described but this was not unexpected in view of the numbers concerned. There was, however, one patient of interest in the pilot study referred to in the introduction. No problem with intubation was anticipated as a result of her pre-operative assessment but, at laryngoscopy, there was no view of the glottis at all. This was because of a vallecular cyst, estimated to be 1 cm in diameter, at the base of the anterior surface of the epiglottis, which forced the epiglottis backwards. It was eventually possible to intubate the larynx with the leading edge of the epiglottis hooked up with a bougie; the tracheal tube was slipped behind it and directed blindly towards the larynx. Despite the problem with direct visualisation, it was easy to confirm that the tube was located satisfactorily in the larynx using the preliminary form of the tactile test.

Table 2. Frequency of successful testing relative to sex and the presence or absence of dental block. Dental block is defined as the presence of lower left molar teeth.

	Females		Males	
	No dental block (n = 41)	Dental block (n = 78)	No dental block (n = 52)	Dental block (n = 29)
Test 1 positive	100%	96.1%	98.1%	65.5%
Test 2 positive	80.5%	70.5%	90.4%	41.4%
Neither test positive	0	1	0*	5*

* Significant difference, $p < 0.01$.

Table 3. Measured distances (mm) in 200 patients.

	Mean distance (SD)	Range
Mouth opening	38.9 (6.5)	25–60
Interarytenoid width (n = 112)*	10.6 (3.4)	4–20
Corner of mouth to hyoid	84.6 (9.5)	70–105
Arytenoid to hyoid (n = 154)†	10 (3.6)	5–20
Upper incisors/gums to tip of epiglottis	86.3 (13)	47–105

* Measured only when competitive muscle relaxants used.
† Sometimes only within reach after displacement.

Discussion

The practical possibility of a reproducible confirmation of orotracheal tube placement in the larynx by a tactile method is, as far as the authors have been able to discover from the literature, quite novel. This is surprising, since a number of methods for tactile oral intubation have been reported.[11–14] Most of these describe some way of elevating the epiglottis and then guiding the tracheal tube blindly onwards toward the larynx. Sykes[12] did mention that occasionally the arytenoids could be felt but also implied that it was not always possible to reach the epiglottis.

It is the belief of the authors that, when properly implemented, the TOP test may prove to be an important addition to the tests currently used to check tracheal tube placement. The attraction of using the interarytenoid groove as the main target, is that it is impossible to imagine anything else having quite the same feel to it, once this is learnt. Each of the authors achieved a similar success rate with the tests.

Naturally, the tests have some limitations. The narrowest mouth opening in the patients studied was 25 mm and this presented no problem when the tests were performed. However, application of the tests to large males with a full set of teeth resulted in a reduced success rate. So far, the problem of the anaesthetist with small hands has not been investigated.

Difficult intubation

None of the patients in the main series presented difficulty in intubation, so it is possible only to speculate about how useful this test will prove in that circumstance. The success in the patient with a vallecular cyst gives grounds for optimism in this respect. These cysts are not common but they can cause respiratory obstruction[15] and problems at induction of anaesthesia.[16]

Murrin[17] reported that inability to visualise the larynx is most commonly associated with the following features: short muscular neck (bull neck); receding mandible; prominent upper incisors; narrow mouth with a high, arched palate; limited movement of the mandible; and large breasts. Of these features, only limited movement of the mandible is likely to be of importance in respect of increased difficulty in performance of the TOP test.

It must be stressed that practical experience with the test is important. This encourages not only a certainty about the feel of the structures palpated, but also a confidence in testing more difficult patients. It is not recommended that the tests should be tried for the first time in dire circumstances when the examiner has no previous experience of their use.

Obstetric anaesthesia

The tests have potential uses in obstetric anaesthesia. Oesophageal misplacement remains an important cause of maternal deaths in the latest *Confidential Enquiry into Maternal Deaths*.[18]

Applied cricoid pressure might be considered to have the potential to interfere with the tests but this does not seem to be the case, although the function of the examiner's left hand in performance of either test is substituted by the assistant pressing on the cricoid cartilage. Upward movement of the larynx via the cricoid cartilage is not inappropriate; indeed, it is common practice to do this when there is any difficulty in visualisation of the cords. Rotational movements of the cricoid, however, are not advised, since the effectiveness of the oesophageal compression may diminish as a result. Experience shows that identification of the interarytenoid groove is feasible even when cricoid pressure is applied.

Teaching of applied anatomy

The experience gained in further understanding of the mobility of the relevant anatomical regions during this study, was felt to be most informative. Cormack and Lehane[10] made references to mobility of the soft tissue at the base of the tongue but Boliston[19] later suggested that this should have been categorised specifically as one of the factors that cause difficulty in intubation. The present authors would endorse this view.

Training junior anaesthetists

Most anaesthetists have felt the need to check the intubations performed by juniors under their training. The only certain way to do this at present is by re-introducing the laryngoscope for a second look. The TOP tests may have an advantage in this situation as they are probably less traumatic, almost certainly quicker and equally re-assuring when confirmatory.

Considerations for practical implementation

The tests are simple in use once learned. Both the authors found that, towards the end of the series, it was usual for both parts of the test to be completed in less than 10 seconds and, in normal practice, only one confirmation is required. The most important essential is an ability to recognise the relevant soft tissues by palpation, in particular the interarytenoid groove. It is best to start with edentulous patients, in whom the tests are easier to perform. Careful attention to the details outlined in the formal description of the tests is required for the more difficult cases.

It should be appreciated that the arytenoids are important structures and that tangential forces on them must be avoided during an examination. As far as possible, the relevant structures should be identified without vigorous manipulation.

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Effects of benzodiazepines on laryngeal reflexes

Comparison of lormetazepam and Diazemuls

N. D. GROVES, J. L. REES AND M. ROSEN

Summary

Of 20 volunteers, five were given intravenous Diazemuls 15 mg over 15 seconds, and three groups of five were given lormetazepam 2 mg intravenously over 10, 20 and 60 seconds, respectively. Laryngeal reactivity and psychomotor function were tested at intervals from prior to injection until 4 hours after injection. For equivalent degrees of depression of psychomotor function, lormetazepam depressed the laryngeal reflex less than Diazemuls ($p = 0.004$). Lormetazepam given over 60 seconds depressed the laryngeal reflex more than when given over 10 seconds ($p = 0.008$) or over 20 seconds ($p = 0.048$), although a significant difference was not demonstrated between the 10-second and 20-second groups. These results concur with experimental evidence that benzodiazepine receptor multiplicity exists, which allows various members of the benzodiazepine group of drugs to exhibit differing therapeutic ratios for their various effects.

Key words

Hypnotics, benzodiazepines; lormetazepam, diazepam.
Larynx; reflexes.

Benzodiazepines produce a number of effects which include sedation, hypnosis, anxiolysis and muscle relaxation; they are also anticonvulsant.[1] Some anaesthetists hold that the only real differences between the various members of the group are pharmacokinetic ones,[2] especially in view of the large number of active metabolites involved, but many people consider that the individual drugs may have individual pharmacological profiles. For instance, equally sedative doses of two benzodiazepines might have differing degrees of anxiolytic activity. Unfortunately, many of the effects of benzodiazepines are not amenable to exact measurement.

It was noted during a previous study which compared the recovery of psychomotor function in patients who received intravenous diazepam (Diazemuls), midazolam or lormetazepam for outpatient fibreoptic oesophagogastroduodenoscopy, that those patients given lormetazepam were particularly intolerant of the gastroscope, although apparently satisfactorily sedated.

The present study was designed with two aims: firstly, to investigate whether equally sedative doses of Diazemuls and lormetazepam depress the laryngeal reflexes to an equal extent and, secondly, to investigate unpublished observations that the effect of lormetazepam might be altered by varying the speed of injection. The opportunity was also taken to see whether there was

N.D. Groves, MRCP, FFARCS, Lecturer, J.L. Rees, BSc, Research Fellow, M. Rosen, MB, ChB, FFARCS, Honorary Professor and Consultant, Department of Anaesthetics, University Hospital of Wales and University of Wales College of Medicine, Heath Park, Cardiff CF4 4XW.

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any difference in pain during injection between the drugs or which might be related to various injection speeds of lormetazepam.

Methods

Approval for the study was obtained from the Joint Ethical Committee of the University of Wales College of Medicine and South Glamorgan Health Authority. Twenty volunteers were recruited and gave informed, written consent. They were aged between 18 and 40 years, were ASA class 1 or 2 and were nonsmokers. Volunteers taking any intercurrent drug therapy were not studied. Each was asked to avoid alcohol from noon on the day preceding the trial.

The volunteers were divided into four groups of five: groups 1, 2 and 3 to be given lormetazepam 2 mg intravenously over 10, 20 and 60 seconds, respectively, and group 4 to be given Diazemuls 15 mg intravenously over 15 seconds; this period falls between the lormetazepam 10- and 20-second groups. The drugs were administered via indwelling cannulae sited in the forearm, in a double-blind fashion, according to a randomised programme. Double-blinding was achieved by shielding the injection site from the volunteer and by having a researcher otherwise unconnected with the trial to read the programme and administer the drug.

Laryngeal reactivity and psychomotor function tests were performed prior to drug administration, to establish baseline data. Following the drug, laryngeal reactivity was measured at 15-minute intervals for 90 minutes, and then at 30-minute intervals for a further 150 minutes. Psychomotor tests were performed the day before the experiment, prior to drug administration and at 30 minutes, 2 hours and 4 hours after drug administration.

Subjects were asked to mark on a linear analogue scale, the degree of any pain associated with injection of the drug. The scale ends were labelled 'No pain at all' and 'The most pain you can imagine'.

Results for each volunteer were expressed as a percentage of the baseline reading where appropriate, so that mean values for each group could be constructed. Results were analysed using the Kruskal–Wallis one-way analysis of variance and the Mann–Whitney U test; $p < 0.05$ was taken to indicate a significant difference. Results from the psychomotor testing were subjected to analysis of variance.

Testing laryngeal reactivity

The protective reflex of the larynx, the Kratschmer reflex, is evoked by a mechanical or chemical stimulus, via receptors located in the hypopharynx and larynx.[3] Afferent pathways travel in both parasympathetic and sympathetic nervous systems and the motor function that results is a temporary closure of the vocal cords.[4] The sensitivity of the reflex is reduced by age,[4] by certain depressant drugs[5] and also by tracheal intubation,[6] but for any particular subject the reflex can be shown to occur consistently at the same level of stimulation.

A mechanical stimulus is difficult to reproduce experimentally and so a chemical stimulus is used to test the laryngeal reflex. The test used was a modification of one originally described by Pontoppidan and Beecher.[4] Subjects were asked to breathe air from an 8-litre Collins water spirometer via a breathing system and nonrebreathing valve (Fig. 1). The breathing system contained an injection port approximately 200 ml proximal to the mouthpiece. Through this port, 50-ml air boluses that contained various concentrations of ammonia gas were injected in double-blind fashion, as the researcher who performed the injection was shielded both from the volunteer and from a second researcher who monitored the spirometer trace. The boluses were stored, prior to injection, in a battery of 50-ml ground-glass syringes, in which they had been produced by drawing in various amounts of 1.6% ammonia gas from a gas bag (volumes ranged from 2–20 ml of 1.6% ammonia gas), and topping up to 50 ml with air. This procedure was followed so that all injections of gas into the breathing system would be of the same volume, regardless of ammonia content. Injections into the breathing system were made prior to the start of inspiration.

Amounts of ammonia sufficient to elicit the laryngeal reflex cause a brief, temporary closure of the vocal cords, the 'glottic stop', and this may be seen as a brief step on the inspiration flow trace of a spirometer. The smallest amount of ammonia required to elicit the laryngeal reflex, was labelled the 'threshold dose'. The size of this dose increases as the laryngeal reflex is depressed. Doses smaller than the threshold dose cause no appreciable interruption to inspiration.

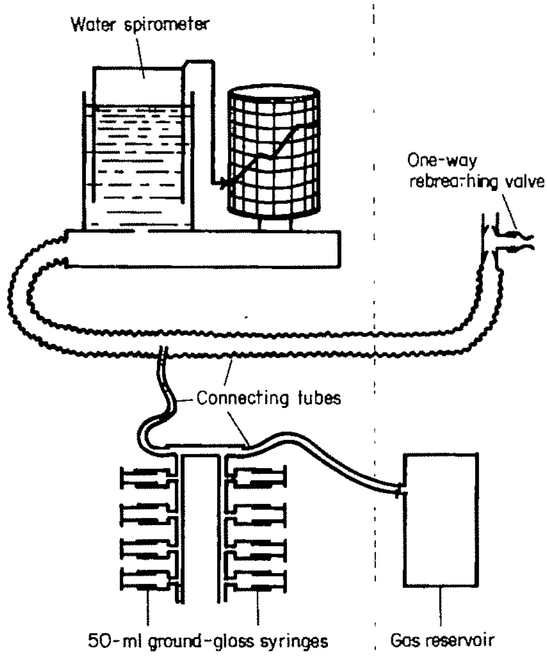

Fig. 1. Apparatus for testing the laryngeal reflex. The volunteer breathes air via a one-way valve from a water spirometer. Boluses of ammonia gas are added to the breathing system using a battery of ground-glass syringes.

Results

The mean threshold dose of ammonia for the 150 minutes of the trial following drug injection was found for each volunteer. Using this figure, the four groups were compared with each other. Firstly, there was a significantly greater depression of the laryngeal reflex with Diazemuls 15 mg given over 15 seconds, compared with lormetazepam 2 mg given over 10 seconds ($p = 0.004$) and with lormetazepam 2 mg given over 20 seconds ($p = 0.004$).

There was no significant difference between the 10-second and 20-second lormetazepam groups but both these groups showed significantly less depression of the laryngeal reflex than did the group given lormetazepam 2 mg over 60 seconds ($p = 0.008$ and $p = 0.048$, respectively).

The mean threshold doses required by each group of volunteers at each test point are illustrated in Figs. 2–5. An increase in the threshold dose of ammonia reflects a depression of the laryngeal reflex. The large error bars in the lormetazepam 60-second group appear because one member of the group showed much greater depression of laryngeal reflex than the other four, although re-analysis of the data after exclusion of this volunteer's results did not alter the significance levels quoted above. The large error bars in the Diazemuls group represent a more general variability within that group.

Most of the psychomotor tests showed a significant or near significant difference, over time, between the three test points after the drug was given, which reflects recovery of psychomotor function. Only two of the 11 tests administered showed any significant difference between drugs; the visualisation and visual search tests both indicated that the lormetazepam dose administered was more sedative than the Diazemuls ($p = 0.025$).

Linear analogue scales did not reveal a significant difference in pain on injection between any of the four groups.

Discussion

This trial has demonstrated that two benzodiazepines that produce equivalent sedation, may cause differing degrees of depression of the laryngeal reflex. This observation is not without

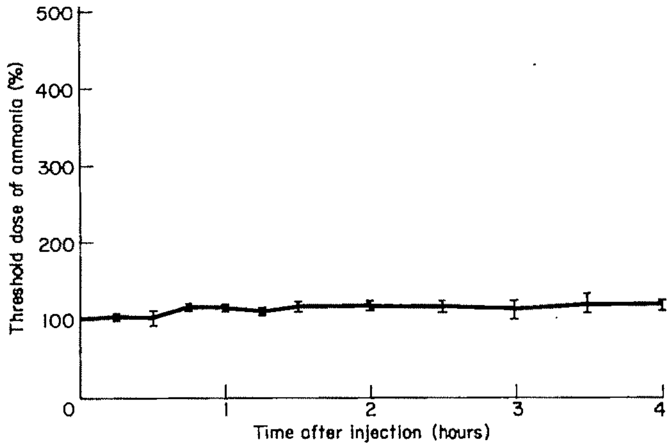

Fig. 2. Group 1 (lormetazepam, 10 seconds). Mean and SE of threshold dose of ammonia required by the five subjects at each sampling point (abscissa) expressed as a percentage of the baseline threshold dose (ordinate).

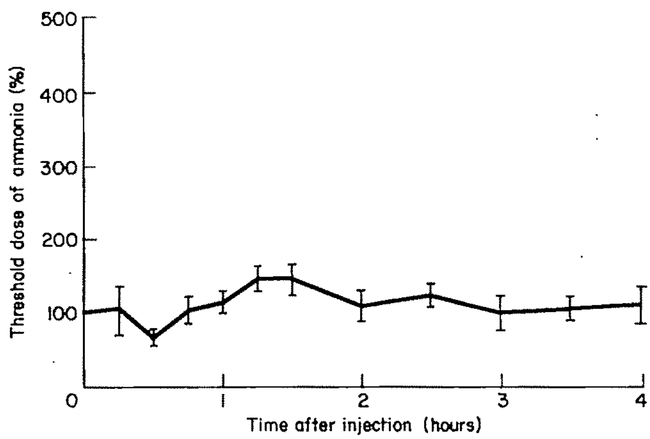

Fig. 3. Group 2 (lormetazepam, 20 seconds). Data displayed as in Fig. 2.

clinical significance. It is desirable to depress the laryngeal reflex in some circumstances, for instance during endoscopy, and a drug such as lormetazepam would not be a good choice.

However, in many other situations, laryngeal depression during sedation is undesirable, since it makes pulmonary aspiration of gastric contents more likely, especially in patients in whom there is already an increased risk of gastric reflux. For instance, risk of reflux is increased by delayed gastric emptying, some causes of which, such as morphine, pethidine or diazepam, increase risk of reflux further through reduction of lower oesophageal pressure tone.[7] A drug such as lormetazepam would be advisable if sedation was required in these circumstances.

Blitt *et al.*[8] showed that general anaesthesia led to silent regurgitation in 7.8% of patients, of whom 8.6% showed evidence of pulmonary aspiration. Thus it could be argued that a benzodiazepine which preserves the laryngeal reflex, is preferable as premedication to one which does not.

Duckett and Hirsh[6] demonstrated reduced laryngeal reflexes for many hours postoperatively in patients who were intubated during

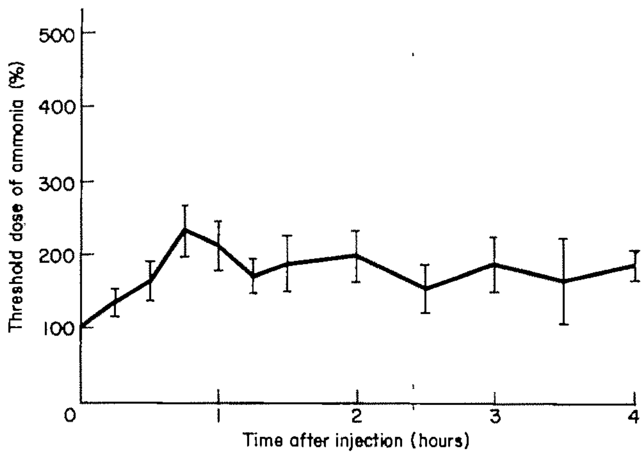

Fig. 4. Group 3 (lormetazepam, 60 seconds). Data displayed as in Fig. 2.

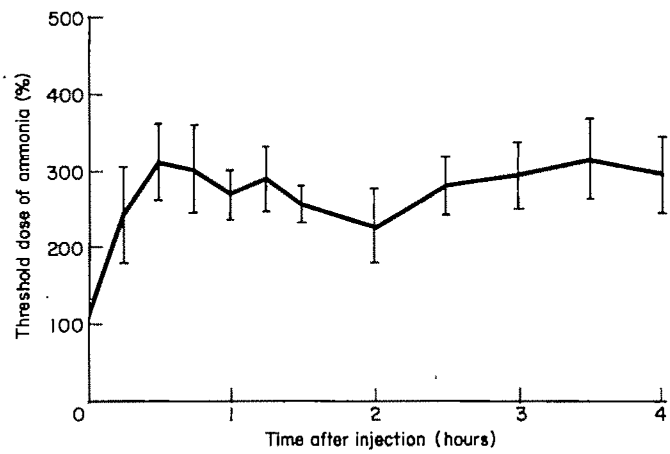

Fig. 5. Group 4 (Diazemuls, 15 seconds). Data displayed as in Fig. 2.

surgery. However, they did not specify which of the three nonintubated patients, one of whom received general anaesthesia and the other two, regional anaesthesia with intravenous sedation, was the one who also had prolonged depression of the laryngeal reflex. This leaves open the possibility that general anaesthesia, rather than intubation, was responsible. In such circumstances, a sedative drug which further depressed the laryngeal reflex should be avoided.

A further relative contraindication to the use of sedatives which depress the laryngeal reflex is increasing age, since Pontoppidan and Beecher[4] showed that increasing age is related to decreased laryngeal reactivity.

Unfortunately, whether a patient's laryngeal reactivity has been significantly reduced by any particular drug or event, is not easily measurable subsequently since there is a wide between-patient variability in the dose of ammonia required to elicit the glottic closure. Hinkle and Tantum[3] stressed the need for control readings to allow interpretation of subsequent measurements in any particular patient.

Our results are in contrast to those in a recent publication[9] which concluded that lormetazepam was preferable to Diazemuls as a premedication prior to endoscopic procedures because it had a shorter elimination time and produced greater anxiolysis. However, although objective

psychometric testing was performed in that trial, only subjective assessment was made of sedation and quality of operating conditions. Also, drug doses administered varied by up to 100%: up to 50% due to weight differences, and up to 50% due to the condition of the patient.

The differences we have demonstrated between lormetazepam and Diazemuls, might be due to the existence of benzodiazepine receptor multiplicity. Experimental evidence, for instance by heat inactivation of receptors, or displacement of benzodiazepines by other chemicals, shows that any particular benzodiazepine binds selectively to a variety of subgroups of benzodiazepine receptors. These subgroups subserve different physiological functions and are probably coded by separate genes that allow for the existence of selective ligands.[10–12]

Both peripheral type and brain specific benzodiazepine receptors exist.[10] The brain specific benzodiazepine receptors are linked to gamma-amino butyric acid (GABA) receptors. GABA is an inhibitory transmitter and benzodiazepines act by enhancement of GABA transmission. GABA is phylogenetically one of the oldest neurotransmitters and, during evolution, vertebrates have developed a multiplicity of GABA receptors which may be distinguished by their differing binding affinities for various ligands. The GABA benzodiazepine receptor complexes represent a subclass of GABA receptors, which further extends the variety of benzodiazepine receptors.

Furthermore, it is recognised that there are three groups of benzodiazepine receptor ligands, tentatively named agonists, antagonists and inverse agonists.[13–15] Agonists produce classical benzodiazepine effects, antagonists bind to benzodiazepine receptors and inhibit any activity by the other two groups, and inverse agonists act to produce effects opposite to those of the agonists. Some drugs may also combine agonist and antagonist properties.[15]

All this evidence makes it likely that drugs which act at benzodiazepine receptors may produce a variety of effects that depend on the particular drug. Unfortunately, many manifestations of benzodiazepine action are difficult to quantify, such as anticonvulsant activity. Depression of the laryngeal reflex is, however, measurable and our results show different therapeutic ratios for Diazemuls and lormetazepam when depression of laryngeal reflex and sedation are compared. Lormetazepam is a 3-hydroxybenzodiazepine, a subgroup which also includes lorazepam, temazepam and oxazepam, and there are probably slightly different pharmacological profiles for each subgroup of benzodiazepines, and for each member of a subgroup.

The fact that speed of injection of lormetazepam appeared to alter its effects on the laryngeal reflex, is more difficult to understand. Drugs attach by electrostatic bonds to plasma proteins. Heavy protein binding leads to a low free plasma concentration of a drug and hence slow intravenous injections of these drugs are said to have less effect than fast ones.[16] However, intravenous administration of drugs results in plasma concentrations which change too rapidly for equilibration to occur, and the kinetics of disposition are often too complex to evaluate.[17] In these circumstances, the plasma concentrations do not necessarily reflect the concentration at the site of action.

After intravenous injection, lormetazepam levels in plasma fall in three dispositional phases, with half-lives variously reported as 5 minutes, 2.5 hours and 11 hours,[18] or 3 minutes, 45 minutes and 5.4 hours.[19] It may be that the profile of the short first phase of redistribution is altered by variation in the injection speed, and that this might lead to varying amounts of bioavailability. The first two phases of disposition represent redistribution to extracellular space and to tissues, respectively. In plasma, lormetazepam is approximately 88% protein-bound and the drug also has a high affinity for tissues, indicated by its high volume of distribution (6.8 litres/kg).[19] It may be that alteration of the speed of injection leads to a slight alteration in redistribution fractions, which results in a significant change in concentration in the relatively small, free plasma component.

The majority of a dose of lormetazepam is excreted as the conjugate by the kidneys. Only a small amount is *N*-demethylated to the active metabolite lorazepam and it does not seem likely that alterations in this process, as a result of varied injection speed, would produce different measured effects of the drug.

This study has demonstrated two facts. Firstly, lormetazepam given in equally sedative doses at comparable injection speeds, causes less depression of the laryngeal reflex than Diazemuls. Secondly, the effects of a dose of lormetazepam can be varied by altering the speed of injection of

the drug. It would be worth testing this difference with other benzodiazepines. Lormetazepam is clearly not a good choice for those endoscopies which require pharyngeal reflexes to be depressed but, on the other hand, it should be an especially safe drug when used in situations where there is any increased risk of gastric regurgitation and pulmonary aspiration.

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Anaesthesia for laparoscopy

A comparison of five techniques including propofol, etomidate, thiopentone and isoflurane

P. M. R. M. DE GROOD, J. B. M. HARBERS, J. VAN EGMOND AND J. F. CRUL

Summary

This is a report about five anaesthetic techniques for laparoscopy. Propofol and etomidate were used for total intravenous anaesthesia. Propofol, etomidate and thiopentone were used as induction agents prior to inhalational anaesthesia with isoflurane and nitrous oxide. Fentanyl was used for analgesia. Induction with propofol and thiopentone was rapid. Etomidate induction was characterised by myoclonus. Maintenance was smooth with inhalational anaesthesia. Of the groups that received total intravenous anaesthesia, propofol provided stable anaesthesia but required extra bolus doses. Recovery was the most rapid following total intravenous anaesthesia with propofol. Postoperative side effects were much lower after propofol. No difference was observed between the groups with regard to changes in arterial blood pressure and heart rate.

Key words

Anaesthesia, intravenous; propofol, etomidate, thiopentone.
Anaesthetics, inhalational; isoflurane.

Recently propofol (2,6-di-isopropylphenol, Diprivan) has been introduced into clinical practice in some countries in Europe. Over the last two years several studies have demonstrated its properties as an induction agent[1–3] and as an agent for total intravenous anaesthesia.[4–6] Smooth induction in one arm–brain circulation time and a rapid, uneventful recovery are the most obvious properties. Pain on injection,[7–9] decrease in arterial blood pressure[10,11] and a high incidence of apnoea are considered to be disadvantages.

Comparisons of propofol with etomidate, methohexitone and thiopentone have been published for several surgical procedures.[2,3,6,9,10,12,13] Propofol has also been studied in combination with inhalational anaesthetics.[13,14] The different types of procedures and different methodology make comparison between techniques possible only in general terms.

This study was performed to evaluate five anaesthetic techniques for a standard laparoscopy procedure. Propofol and etomidate were used as part of a total intravenous anaesthesia (TIVA) technique. These two agents, as well as thiopentone, were used as induction agents for an inhalational technique with isoflurane. Evaluation and comparison of the induction properties, stability of anaesthesia, speed of recovery and postoperative complications, were the main aims of this study.

P.M.R.M. de Grood, MD, PhD, Staff Member, J.B.M. Harbers, MD, Research Fellow, J. van Egmond, PhD, Staff Member, J.F. Crul, MD, PhD, FFARCS, Professor and Chairman, Institute for Anaesthesiology, St. Radboudziekenhuis, Catholic University of Nijmegen, Geert Grooteplein Zuid 10, 6525 GR Nijmegen, The Netherlands.

Methods

After verbal consent, 76 unpremedicated female patients (ASA grades 1–3) scheduled for laparoscopy were included in this study, which was approved by the hospital ethical committee. The patients had no history of allergy to the drugs used in this study, or evidence of atopy. No patient with a history of serious hepatic, renal, haematological or metabolic disease was included.

An indwelling cannula was inserted in a large vein on the dorsum of the hand or forearm on arrival in the operating room and connected to an infusion of Ringer's solution. The electrocardiogram and finger plethysmogram were continuously monitored. Arterial pressure was measured using an automatic noninvasive blood pressure monitor (Dinamap). The baseline values of arterial pressure and heart rate were measured before induction and subsequently 2 minutes after induction and at 5-minute intervals thereafter.

The patients were randomly allocated into five groups. In group 1, propofol 2.5 mg/kg was used for induction followed by a continuous infusion at a rate of 12 mg/kg/hour for the first 15 minutes, then 9 mg/kg/hour for another 25 minutes and thereafter 6 mg/kg/hour. In group 2, etomidate 0.3 mg/kg was used for induction followed by a continuous infusion of 1.8 mg/kg/hour for the first 15 minutes, 1.5 mg/kg/hour for the next 25 minutes and 1.0 mg/kg/hour thereafter. Propofol was given in undiluted form (10 mg/ml) and etomidate was used as 2 mg/ml solution (4 ml of 125 mg etomidate base/ml of ethyl alcohol, diluted to 250 ml with normal saline). Both drugs were administered using a calibrated syringe pump for the whole of the procedure.

In groups 3, 4 and 5, anaesthesia was induced respectively with propofol 2.5 mg/kg, etomidate 0.3 mg/kg and thiopentone 5 mg/kg. Anaesthesia was maintained with a nitrous oxide–oxygen mixture (2:1) and isoflurane, initially at a concentration of 2%, decreased to 1% after 5 minutes and then maintained until the end of the procedure.

A bolus dose of fentanyl 0.1 mg was administered 60 seconds prior to induction for all groups. Further bolus doses of fentanyl 0.05–0.1 mg were given on signs of painful reactions to surgical stimuli. An extra bolus dose of the induction agent was given on signs of lightening of anaesthesia, such as sweating, lacrimation and cardiovascular changes or movements not related to painful stimuli. The bolus doses of propofol were 0.5 mg/kg, etomidate 0.06 mg/kg and thiopentone 0.3 mg/kg. Suxamethonium 1 mg/kg was given to facilitate tracheal intubation and a further bolus dose of 25 mg if needed. The lungs of all patients were mechanically ventilated, the TIVA groups with a mixture of oxygen and air and for the others with nitrous oxide and oxygen.

Onset of induction was defined in two ways: as the interval between start of administration of the hypnotic agent and cessation of counting, and as the interval between start of administration of the hypnotic agent and disappearance of the eyelash reflex. Two recovery times were defined: the interval from stopping administration of the hypnotic agent until opening eyes on command, and that until simple questions were answered correctly. Recovery of anaesthesia was assessed by the Steward score[15] 5, 15 and 30 minutes after the patients opened their eyes on command. Patients performed a pencil–paper test[16] pre-operatively, one hour and 3 hours postoperatively. The scores were calculated as percentages of the pre-operative values. All patients were visited on the first postoperative day and the incidence of side effects, perioperative awareness and venous sequelae evaluated.

All side effects were recorded from induction of anaesthesia up to 24 hours postoperatively. The intensity of pain on injection was scored as mild, moderate or severe depending on the response of the patient to questioning: mild when a slightly painful sensation was noted, moderate if discomfort was indicated on enquiry and severe if spontaneous complaints were made. Depth and smoothness of anaesthesia were evaluated postoperatively with regard to the need for additional bolus doses of the induction agent, fentanyl or suxamethonium.

The statistical calculations were carried out using the SPSS routine package (SPSS Inc., Chicago, IL). Analysis of variance as well as one-way analysis of variance with the Tukey-HSD procedure were used to analyse differences between groups. Comparisons of incidences were performed by the Chi-squared test or Fisher's exact test (in a 2 × 2 table). In statistical tests $p < 0.05$ was considered significant.

Table 1. Demographic data: values expressed as mean (SD).

Group	Age, years	Weight, kg	Height, cm	Anaesthetic time, minutes	Surgery time, minutes
1 (n = 16)	30.4 (4.3)	63.7 (10.0)	167.8 (6.2)	35.2 (9.3)	25.6 (9.3)
2 (n = 15)	31.0 (3.8)	63.3 (12.9)	165.4 (7.1)	29.8 (10.9)	18.6 (9.7)
3 (n = 15)	32.3 (8.3)	66.0 (11.3)	166.3 (7.7)	33.9 (19.3)	23.5 (19.3)
4 (n = 15)	33.5 (7.2)	65.6 (10.6)	165.1 (6.4)	29.7 (8.4)	19.1 (7.2)
5 (n = 15)	30.5 (3.6)	59.2 (7.8)	164.1 (8.1)	25.3 (7.8)	15.3 (7.1)
ANOVA	NS	NS	NS	NS	NS

Analysis of variance (ANOVA) is used to demonstrate differences between groups. NS, Not significant.

Table 2. Induction times and incidence of apnoea.

Induction agent	Time, seconds		Apnoea
	Stop counting	Loss of eyelash reflex	
Propofol (n = 31)	39.5 (35–44)*	49.9 (48–55)	25 (81%)
Etomidate (n = 30)	32.4 (28–37)*	57.3 (45–70)**	19 (63%)
Thiopentone (n = 15)	31.5 (27–36)	37.1 (33–41)**	15 (100%)

Induction times are given with 95% confidence limits in parentheses. One-way analysis of variance is used to demonstrate differences between groups. *, **, Pairs of groups significantly different at the 0.05 level (Tukey-HSD procedure).

Results

All groups were comparable for age, height, weight and duration of surgery and anaesthesia (Table 1).

Induction

Induction was successful in all patients. Cessation of counting took a few seconds longer following propofol. Disappearance of the eyelash reflex, however, occurred much later and was less predictable following etomidate. Induction was most rapid after thiopentone (Table 2). However, four patients in this group showed reactions on intubation, such as increased heart rate and arterial pressure, together with lacrimation and unintentional movements of limbs and shoulders, despite the administration of suxamethonium. This was judged to indicate an insufficient level of anaesthesia for intubation. Apnoea in excess of 20 seconds occurred after administration of the induction dose in all patients induced with thiopentone, compared to 63% given etomidate and 81% who received propofol (Table 2).

Several side effects were noticed during induction (Table 3). In the thiopentone group three patients coughed before intubation. One patient in group 3, who was a heavy smoker, had bronchospasm during intubation. Discomfort on injection was seen in only one patient in the thiopentone group; the site of injection was on the dorsum of the hand in each case. Complaints of pain along the veins were noticed in about 35% of the patients who received etomidate or propofol. In patients who received these drugs, indwelling cannulae were placed on the dorsum of the hand only when there was a large vein available. Only four patients complained of severe pain, two during propofol administration and two during etomidate administration (Table 4).

Table 3. Incidence of side effects during induction.

Side effect	Number of patients		
	Propofol (n = 31)	Etomidate (n = 30)	Thiopentone (n = 15)
Myoclonus	—	12	—
Hiccough	—	3	—
Cough	1	2	3
Bronchospasm	1	—	—

Maintenance

The anaesthetic conditions were suitable for surgery for all patients during the maintenance

Table 4. Incidence of discomfort on injection.

Induction agent	No pain	Mild	Moderate	Severe
Propofol (n = 31)	21 (68%)	5 (16%)	3 (9%)	2 (7%)
Etomidate (n = 30)	19 (63%)	4 (13%)	5 (17%)	2 (7%)
Thiopentone (n = 15)	14 (93%)	0	1 (7%)	0

Criteria are described in the text.

Table 5. Total doses of fentanyl and suxamethonium.

Group	Fentanyl, µg/kg	Suxamethonium, mg/kg
1	3.9 (3.4–4.5)*+‖	1.7 (1.5–1.9)
2	4.4 (3.8–5.1)§**†	1.9 (1.6–2.2)*+
3	2.5 (2.2–2.9)*§	1.5 (1.4–1.7)*
4	2.6 (2.1–3.0)+**	1.5 (1.4—1.6)+
5	3.0 (2.5–3.5)‖†	1.6 (1.5–1.8)

Mean total doses are given with 95% confidence limits in parentheses. One-way analysis of variance is used to demonstrate differences between groups. *, +, ‖, §, **, †, Pairs of groups significantly different at the 0.05 level (Tukey-HSD procedure). Group 1, TIVA with propofol; group 2, TIVA with etomidate; group 3, propofol and isoflurane; group 4, etomidate and isoflurane; group 5, thiopentone and isoflurane.

period. Both TIVA groups needed more fentanyl than with inhalational anaesthesia (Table 5). This was also valid when the groups with the same induction agent but different techniques were compared (respectively group 1 with group 3, and group 2 with group 4).

There was also a difference in the control of depth of anaesthesia between the groups with TIVA and with isoflurane. In group 1, 14 patients needed 19 extra bolus doses of the induction agent and in group 2, 11 patients needed 39 extra doses; this indicates that in the latter group, the prescribed dose regimens for infusion were insufficient to control depth of anaesthesia. Of the total of 45 patients given isoflurane, only six needed an extra bolus of the induction agent. More supplemental doses of suxamethonium (a total of 13) were needed to control involuntary movements and coughing in patients in group 2. The overall assessment of the quality of maintenance was poor in six patients in group 2 and in one patient in group 3 (Table 6). The latter was the patient with bronchospasm, mentioned above.

Table 6. Quality of maintenance.

Group	Good	Adequate	Poor
1 (n = 16)	11 (69%)	5 (31%)	0
2 (n = 15)	6 (40%)	3 (20%)	6 (40%)
3 (n = 15)	13 (88%)	1 (6%)	1 (6%)
4 (n = 15)	13 (87%)	2 (13%)	0
5 (n = 15)	14 (93%)	1 (7%)	0

Group 1, TIVA with propofol; group 2, TIVA with etomidate; group 3, propofol and isoflurane; group 4, etomidate and isoflurane; group 5, thiopentone and isoflurane.

Recovery

Those patients induced with thiopentone and maintained with isoflurane took longer to open their eyes on command. The most rapid recovery followed TIVA with propofol. TIVA with etomidate resulted not only in the longest time for complete recovery of consciousness, as indicated by reply to simple questions, but recovery was also less predictable, as indicated by the 95% limits of confidence (Table 7).

Table 7. Recovery times and results in pencil–paper test.

Group	Eyes open, minutes	Answering questions, minutes	Pencil–paper test 1 hour	3 hours
1 (n = 16)	7.9 (6–10)*	8.6 (6–11)+§	65 (7)	81 (6)
2 (n = 15)	13.8 (9–19)	19.3 (12–25)§**	53 (6)	86 (4)
3 (n = 15)	9.7 (6–13)	11.3 (7–15)**	77 (7)	82 (6)
4 (n = 15)	12.9 (9–16)	15.5 (11–20)	60 (10)	100 (12)
5 (n = 15)	15.8 (12–20)*	18.0 (14–22)+	43 (8)	77 (8)

Recovery times are given as minutes from end of anaesthesia with 95% confidence limits in parentheses. One-way analysis of variance is used to demonstrate differences between groups. *, +, §, **, Pairs of groups significantly different at the 0.05 level (Tukey-HSD procedure). Pencil–paper test scores are given as percentages of preoperative values with SEM in parentheses. Group 1, TIVA with propofol; group 2, TIVA with etomidate; group 3, propofol and isoflurane; group 4, etomidate and isoflurane; group 5, thiopentone and isoflurane.

There was no difference between groups 1 and 3 for either recovery time. Clinical assessment of recovery, as indicated by the Steward scores, correlated well with the two recovery times. Five minutes after opening their eyes on command, two patients in group 2 and group 4 each had recovery scores below 5, while all other patients scored 5 or more. Ten minutes later, four patients in group 2 and a further four in group 4 had recovery scores below 6. All patients had the maximum recovery score of 6 after 30 minutes. The results of the pencil–paper test are presented in Table 7. There was a high interindividual variation in the performance of the postoperative tests as related to the pre-operative values. Several patients were unable to perform this test one hour after recovery because of impaired psychomotor function or severe side effects, such as nausea or vomiting. After one hour of recovery the mean values for each group did not reach the pre-operative values. Three hours after the end of anaesthesia the mean values varied from 77% to 100%.

Postoperatively, the most important side effects were nausea, vomiting, headache and mental depression. Restlessness and coughing were also observed (Fig. 1). Approximately 60% of the patients in groups 2 and 5 complained of nausea and vomiting. Patients who received propofol had a remarkably low incidence of these side effects. Propofol with isoflurane (group 3) resulted in more nausea and vomiting as compared with the TIVA with propofol (group 1), but the difference was not significant. For the other side effects there was a difference between the patients with inhalational anaesthesia and TIVA, in that the latter was associated with fewer side effects. All patients had comfortably returned to their daily routine activity 24 hours postoperatively.

Cardiovascular variables

Most patients showed an increase of heart rate during the first 10 minutes after induction as compared to their pre-operative values (Fig. 2). These values returned to the baseline and remained stable during the rest of the procedure. After an initial, short-lived increase directly after induction, mean arterial pressure (MAP) decreased below baseline values in the groups with inhalational anaesthesia (Fig. 3). MAP returned to the baseline 10–15 minutes after induction and remained there until the end of procedure. In group 3 the decrease of MAP was more than 25% compared with the baseline values, 7 and 8 minutes after induction of anaesthesia. No significant changes in MAP were seen in the TIVA groups during induction or during maintenance.

Discussion

It has been reported that the relative potency of propofol as compared to thiopentone is

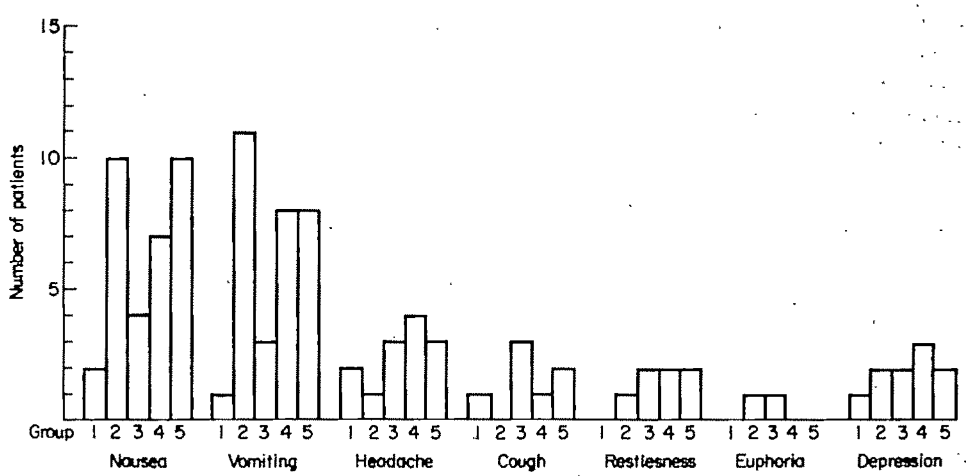
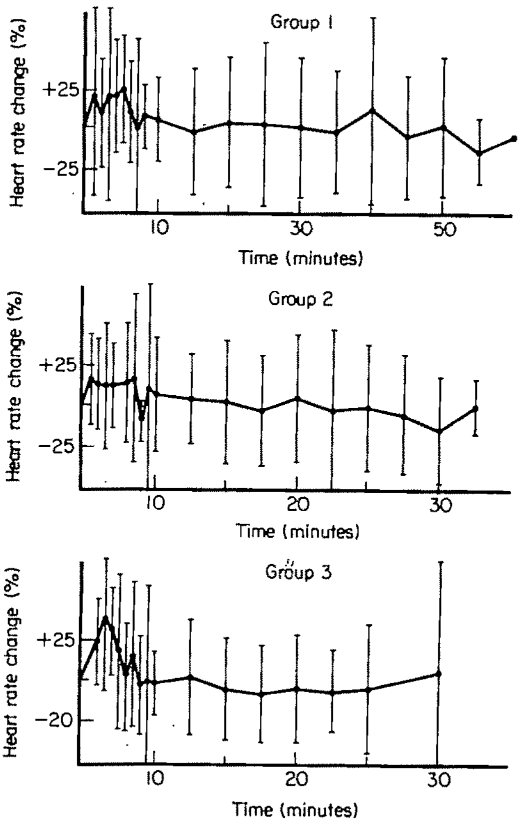


Fig. 1. Side effects during the first 3 hours postoperatively. Group 1, TIVA with propofol; group 2, TIVA with etomidate; group 3, propofol and isoflurane; group 4, etomidate and isoflurane; group 5, thiopentone and isoflurane.



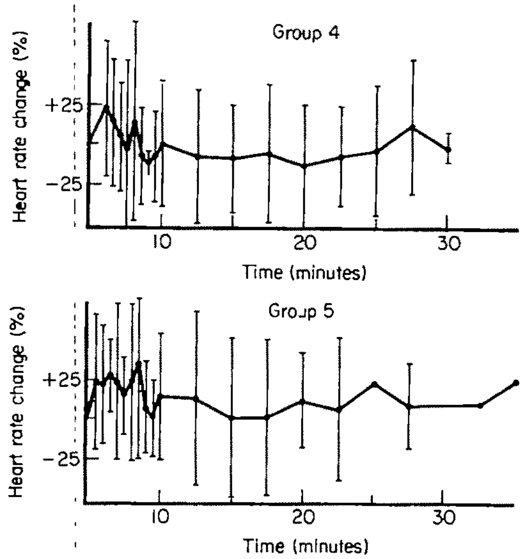


Fig. 2. Heart rate during surgery as percentage change related to pre-operative values. Group 1, TIVA with propofol; group 2, TIVA with etomidate; group 3, propofol and isoflurane; group 4, etomidate and isoflurane; group 5, thiopentone and isoflurane.

1:1.6.[17] In spite of the ratio of 1:2 in this study, four patients (out of 15) induced with thiopentone showed a level of anaesthesia too light at tracheal intubation, compared to one patient (out of 31) who had propofol. Others, using the same doses as in this study, failed to demonstrate differences in induction time between propofol and thiopentone with regard to cessation of counting.[13] No differences were demonstrated in induction time as regards loss of the eyelash reflex when etomidate (0.2 mg) and the Cremophor formulation of propofol (1.5 mg) were compared.[12] There was no difference with the emulsion formulation, between etomidate 0.3 mg and propofol 2.0 mg for both induction times after a pre-induction dose of alfentanil.[6] Differences were found in this study for both induction times but these are fast for all three agents and the differences are of minor clinical importance. The incidence of myoclonus during induction with etomidate was still high, although a pre-induction dose of fentanyl was given.

The anaesthetic agents used for TIVA have to replace inhalational anaesthetics. Stability was similar to the inhalational groups with the dose regimens used for propofol (group 1), but higher doses of fentanyl were required. Not only isoflurane itself but also the analgesic properties of nitrous oxide have to be replaced with intravenous agents in the TIVA groups. The dose regimens of propofol in group 1 were based on our previous work.[5,6] They were higher than the doses needed to maintain anaesthesia in combination with regional anaesthesia,[18] or needed for a TIVA technique in combination with a continuous infusion of alfentanil.[4] For group 2 (TIVA with etomidate), the dose regimen of etomidate resulted in unstable anaesthesia and, therefore, extra doses of fentanyl were needed as well as extra doses of the induction agent. Most of these extra doses were given in the first part of the surgical procedure. For group 1 the prescribed dose regimen alone was also not sufficient to control the depth of anaesthesia, but the overall conduct was much easier than in

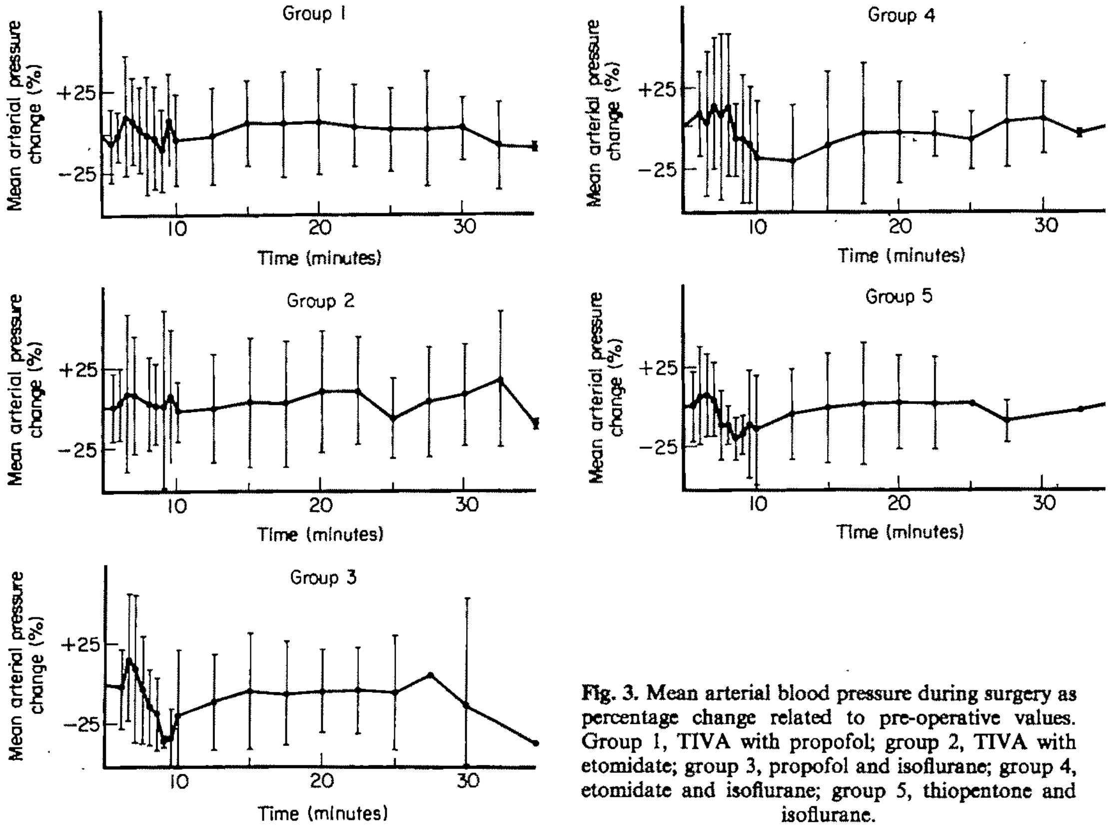


Fig. 3. Mean arterial blood pressure during surgery as percentage change related to pre-operative values. Group 1, TIVA with propofol; group 2, TIVA with etomidate; group 3, propofol and isoflurane; group 4, etomidate and isoflurane; group 5, thiopentone and isoflurane.

group 2. The concentration of isoflurane used in this study is a little lower than the 1.2% reported by Forrest[19] for clinical requirement, but maintenance was very stable with the pre-induction dose of fentanyl 0.1 mg and a supplementary dose of 0.1 mg just before surgery.

Decreases in arterial blood pressure have been reported for propofol and thiopentone.[10,11] Etomidate has been described as cardiovascularly stable.[12] Changes in cardiovascular variables demonstrated during carefully performed studies of the effect of single agents, do not necessarily reflect the everyday situation. The changes in arterial pressure and heart rate showed considerable variation in this study and seemed to be related more to surgical stress than to the effect of the agent itself. The lack of discrepancy between the groups and the absence of an initial decrease in blood pressure may be related to the tracheal intubation, which was performed as soon as possible after induction. In the groups given isoflurane, there was a mean decrease in blood pressure after intubation but before the start of surgery; blood pressure increased to normal values during the procedure. The higher concentration of isoflurane during the pre-surgical period may have contributed to this effect.

Recovery from anaesthesia after propofol was rapid. The recovery times reported here are similar to those reported by others.[4–6,14] As observed earlier, the time between opening eyes on command and answering questions was remarkably short. The slowest recovery was shown after thiopentone–isoflurane anaesthesia and after TIVA with etomidate. Higher doses of etomidate in this last group may lead to more stable anaesthesia but also to longer recovery. Recovery following isoflurane could be expected to be independent of the induction agent. No difference could be demonstrated for these groups by the very sensitive Tukey-HSD procedure. However, after propofol–isoflurane (group 3), the mean recovery times were much shorter than after thiopentone–isoflurane and a little longer than after TIVA with propofol.

Groups 1 and 3 had significantly shorter recovery times as compared with etomidate (group 2).

We used a pencil–paper test to evaluate the progression towards complete recovery. This measures both accuracy and the ability to concentrate, as well as return of psychomotor function.[16] We could not demonstrate statistical differences between any of the groups, mainly as a result of the great interindividual differences in test scores. One hour after the end of administration of the hypnotic agent the mean scores of the patients in the thiopentone group were only 43% of the pre-operative values, while the patients in the propofol–isoflurane group reached 77%. This correlates with the clinical observation that the patients in group 5 suffered more residual effects from the general anaesthesia than the patients in all other groups. There was less difference 3 hours postoperatively and some patients completed this test as well as before operation, but only in group 4 did the patients reach a mean of 100%.

Of the postoperative side effects, nausea and vomiting have the highest incidence. The aetiology of these side effects was reviewed by Palazzo and Strunin.[20] They concluded that, nowadays, the incidence of emetic problems associated with anaesthesia in the absence of antiemetics, is still around 30%. Nitrous oxide, etomidate and fentanyl are agents known to cause vomiting. In a review of 25 clinical studies with propofol, Stark *et al.*[9] reported incidences of vomiting and nausea of 2–2.5%, and about 10–12% for their comparator agents thiopentone and methohexitone. Laparoscopy is known to be associated with a high incidence of nausea and vomiting. Recently, Lonie and Harper[21] reported an incidence of these side effects of about 50% after laparoscopy. Their anaesthetic technique was similar to that used in group 5 in this study, with the exception that enflurane was used instead of isoflurane. This study confirms that propofol anaesthesia is accompanied by a low incidence of nausea and vomiting in spite of the larger doses of fentanyl in group 1 and the nitrous oxide in group 3. The differences between the TIVA and inhalational groups for the other postoperative side effects suggest that they are related to isoflurane.[22]

In conclusion, the new intravenous agent propofol has several advantages over the other anaesthetics used in this study. In particular, the rapid, uneventful recovery makes TIVA with propofol suitable for outpatient laparoscopy but propofol induction followed by isoflurane maintenance provides a more stable technique.

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Comparison of conventional intermittent positive pressure ventilation with high frequency jet ventilation

Studies following aortocoronary bypass graft surgery

J. NORMANDALE, M. PATRICK, K. M. SHERRY AND R. O. FENECK

Summary

This study was designed to compare the cardiorespiratory effects of high frequency jet ventilation at 150 breaths/minute with and without added positive end expiratory pressure, with conventional intermittent positive pressure ventilation in 20 patients following aortocoronary bypass graft surgery. On comparison with intermittent positive pressure ventilation, there was a decrease in peak airway pressure during high frequency jet ventilation when positive end expiratory pressure of 0 or 0.5 kPa was applied, but not with 1 kPa, and an increase in mean airway pressure with positive end expiratory pressures of 0.5 and 1 kPa. On changing from intermittent positive pressure to high frequency jet ventilation with no added end expiratory pressure, there was an acute decrease in arterial oxygen tension and increases in cardiac output and total tissue oxygen delivery. On changing from intermittent positive pressure ventilation to high frequency jet ventilation with 1 kPa of positive end expiratory pressure, there was an acute decrease in arterial oxygen tension, cardiac output and oxygen delivery, and increases in pulmonary arterial, right atrial and pulmonary capillary wedge pressures. The addition of positive end expiratory pressure did not prevent the acute decrease in arterial oxygen tension which occurred on transfer to high frequency jet ventilation.

Key words

Ventilation; intermittent positive pressure, high frequency jet.

It is well established that ventilation of the lungs with low tidal volume and at a high respiratory rate provides adequate gas exchange. Recently, a number of methods of delivering high frequency ventilation have been devised; these include high frequency jet ventilation (HFJV) which was introduced by Klain and Smith[1] in 1977. It has been suggested that the advantages of HFJV, in comparison with conventional intermittent positive pressure ventilation (IPPV), include lower peak and mean airway pressures,[2] a reduction in pulmonary barotrauma[3] and less disturbance in cardiovascular function.[4] Such a method of artificial lung ventilation might be ideally suited to patients who are at risk from impaired cardiac performance. End expiratory pressure is usually zero during IPPV unless positive end expiratory pressure (PEEP) is

J. Normandale, FFARCS, Senior Registrar, The Middlesex Hospital, M. Patrick, FFARCS, Senior Registrar, The London Hospital, Whitechapel, K.M. Sherry, FFARCS, Senior Registrar, The London Chest Hospital, R.O. Feneck, FFARCS, Consultant, The London Chest Hospital, London.

Correspondence should be addressed to Dr R.O. Feneck, Department of Anaesthesia, The London Chest Hospital, Bonner Road, London E2 9JX.

applied. PEEP is commonly used in this situation to improve arterial oxygen tension. However, during HFJV at the respiratory rates used in this study, there is a certain amount of PEEP inherent in the system since the expiratory time constant of the lungs and chest wall is exceeded.[5] Nevertheless, the effects of addition of further PEEP to patients who receive HFJV on arterial oxygenation and haemodynamics are less well defined. This work was designed to compare the cardiorespiratory effects of IPPV with HFJV and to establish the role of added PEEP in patients following cardiac surgery. However, patients who undergo cardiac surgery do not constitute one single group and we therefore studied three groups of patients: patients with good left ventricular function scheduled for aortocoronary bypass graft (ACBG) surgery; patients undergoing valve surgery; and a further subgroup with borderline or poor cardiac function. This paper reports the results of studies undertaken on patients with good left ventricular function following ACBG surgery.

Patients and methods

Twenty adult males who presented for elective ACBG surgery and who gave written informed consent were studied. All of the patients had good left ventricular function at cardiac catheterisation and were clinically free from cardiac failure. Pre-operative respiratory function tests were within normal limits.

Relevant anti-anginal therapy was given on the day of surgery and premedication of oral diazepam and intramuscular papaveretum with hyoscine was administered. Anaesthesia was induced using a benzodiazepine and opiate and, following the administration of a muscle relaxant, the trachea was intubated with a tracheal tube designed to facilitate HFJV (Hi-Lo Jet tube, Mallinckrodt). The left radial artery was cannulated and a triple lumen, flow-directed pulmonary artery catheter was introduced via the right internal jugular vein. Radial artery, pulmonary artery and right atrial pressure waveforms were displayed. Body temperature, urine output and standard lead II of the electrocardiogram were monitored throughout the operation and the patient's lungs were ventilated artificially. The patients were transferred to the intensive care unit after surgery.

The study started when the patient's clinical condition had been stable for one hour; i.e. there had been no change in vasodilator therapy, fluid/blood requirements, haemodynamic status or ventilation. In no patient was any alteration in therapy required during the study period.

The patients were assigned randomly to one of two groups, and this designated the sequence in which IPPV and HFJV, with and without PEEP, were to be applied (Fig. 1).

IPPV was delivered using a Brompton–Manley ventilator with a tidal volume (V_T) of 10 ml/kg and an inspiratory:expiratory ratio (I:E) of 1:2.5. Delivered minute volume and system deadspace were manipulated to ensure that arterial carbon dioxide tension ($Pa\text{CO}_2$) was within the range 4.5–5.0 kPa.

HFJV was delivered using an Acutronic MK800 ventilator (Acutronic AG). The system used is shown in Fig. 2. High pressure gas was delivered down the jet lumen of the tracheal tube to the opening 2 cm from the tip, and gas was also entrained from the T-piece. Both driving and entrained gases were heated and humidified; they were derived from the same oxygen/air blender set to deliver 100% oxygen. PEEP was applied to the expiratory limb of the T-piece by a water manometer to provide levels of 0 kPa (HFJV_0), 0.5 kPa ($\text{HFJV}_{0.5}$) or 1 kPa (HFJV_1). The ventilator rate was set at 150 cycles/minute (2.5 Hz) with an inspiratory time of 30% of the respiratory cycle (I:E 1:2.3). The driving gas pressure (and hence total ventilation) was manipulated to maintain $Pa\text{CO}_2$ within normal limits. At least 30 minutes were allowed to elapse following any alteration in ventilation or in applied PEEP, in order to ensure cardiorespiratory stability before a series of readings was taken. The list of measured and derived parameters is shown in Table 1.

Group 1: IPPV HFJV_0 $\text{HFJV}_{0.5}$ HFJV_1 IPPV
Group 2: IPPV HFJV_1 $\text{HFJV}_{0.5}$ HFJV_0 IPPV

Fig. 1. Sequence in which HFJV, with and without added PEEP (0, 0.5, 1 kPa), was applied to patients in groups 1 and 2.

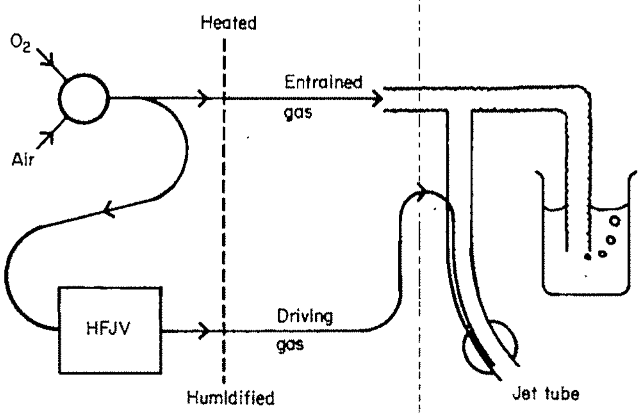

Fig. 2. System used for delivering HFJV (see text for details).

Table 1. List of measured and derived parameters (standard equations were used for derived data).

Measured
Heart rate
Systemic arterial pressure
Pulmonary artery pressure
Right atrial pressure
Pulmonary capillary wedge pressure
Cardiac output
Arterial and mixed venous blood gases, saturation and Hb
Derived
Stroke index
Systemic and pulmonary vascular resistances
Left and right ventricular stroke work indices
Shunt fraction
Total tissue oxygen delivery

Haemodynamic and airway pressures, body temperature and heart rate were recorded using a Patient Data 565A video monitor (Kone UK) interfaced with an Apple IIE microcomputer. Cardiac output was measured by the thermodilution technique and the mean of multiple measurements was recorded. Airway pressure was measured at a point 2 cm below the jet orifice, at the tip of the tracheal tube, using the second lumen provided. Blood gas analysis was performed using an ABL-3 analyser (Radiometer Ltd). Arterial and mixed venous oxygen saturation and haemoglobin concentration were measured using an oximeter (OSM2, Radiometer Ltd). Random duplicate samples were sent to the haematology laboratory for haemoglobin estimation.

Statistical analysis of the data was performed using analysis of variance and Student's t-test (paired and unpaired) as appropriate.

Results

The demographic data are shown in Table 2. The patients were comparable on the basis of body weight, height, surface area, age, vasodilator therapy, blood loss and urine output during the study.

The effects of changing from IPPV to HFJV with increasing PEEP and back to IPPV in patients in group 1, are shown in Figs 3–5. The effects of changing from IPPV to HFJV with decreasing PEEP and back to IPPV in patients in group 2 are shown in Figs 6–8. In each figure, the effect on peak and mean airway pressures (P_{aw}) associated with changing the mode of ventilation and the application of additional PEEP, is shown.

On changing from IPPV to $HFJV_0$ (group 1 patients), there was a significant decrease in peak P_{aw} but mean P_{aw} remained unchanged. There was a significant decrease in arterial oxygen tension (Pa_{O_2}) but cardiac output ($\dot{Q}_t$) and total tissue oxygen delivery (flux) increased;

Table 2. Patient data and vasodilator therapy: values expressed as mean (SEM).

	Group 1 (n = 10)	Group 2 (n = 10)
Age, years	54 (3.2)	50 (3.0)
Weight, kg	79 (2.0)	74 (2.6)
Body surface area, sq. m	1.94 (0.03)	1.84 (0.05)
Blood loss, ml/hour	29	40
Urine output, ml/hour	116	95
Vasodilators		
Sodium nitroprusside	6	6
Glyceryl trinitrate	3	3
None	2	2

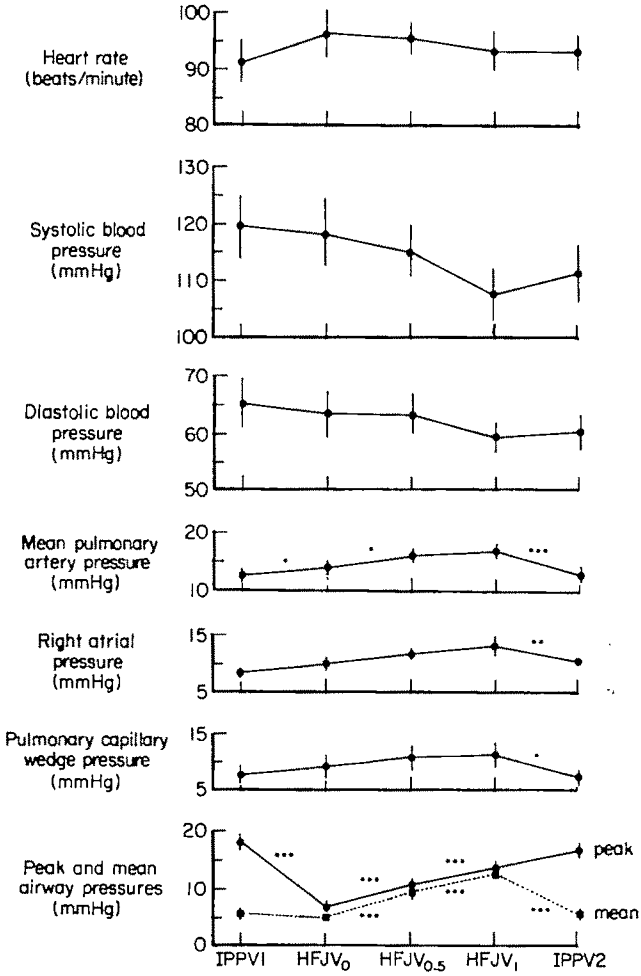

Fig. 3. Effects of transfer in group 1 patients from IPPV to HFJV with gradual application of up to 1 kPa PEEP. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

however, stroke index (SI) and left ventricular stroke work index (LVSWI) remained unchanged. On changing from $HFJV_0$ to IPPV (group 2 patients), there was an increase in peak P_{aw} whereas mean P_{aw} remained unchanged. There were significant decreases in systemic vascular resistance (SVR) and systolic arterial pressure (SAP); however, SI remained unchanged and LVSWI decreased significantly. On changing from IPPV to $HFJV_1$ (group 2 patients), there was a significant increase in mean P_{aw} but peak P_{aw} remained unchanged. There were significant increases in right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP). Pulmonary vascular resistance (PVR) also increased, and LVSWI, $\dot{Q}_t$ and flux all decreased significantly. In each of the parameters described there were mirror-image changes in group 1 patients following transfer from $HFJV_1$ to IPPV but, in addition, SI increased significantly. These changes are shown in Tables 3 and 4. The changes which followed the gradual application of extra PEEP during HFJV to patients in group 1 are shown in Table 5.

The relevance of the data shown in Table 5 is best understood if it is seen in conjunction with Tables 3 and 4; however, it can be seen clearly that the gradual application of PEEP sufficient

Table 3. Mean (SEM) effects of transfer from $HFJV_1$ to IPPV in group 1 patients, and from IPPV to $HFJV_1$ in group 2 patients, on peak and mean airway pressures (P_{aw}), pulmonary artery pressure (PAP), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP).

	Group 1		Group 2	
	$HFJV_1$	IPPV	IPPV	$HFJV_1$
Peak P_{aw}, mmHg	13.6	16.7	16.4	14.1
	(0.9)	(0.9)	(1.7)	(1.2)
Mean P_{aw}, mmHg	12.5***	5.6	4.9***	12.2
	(0.6)	(0.3)	(0.5)	(0.7)
PAP, mmHg	17.5***	13.3	11.8***	17.0
	(0.9)	(0.8)	(1.1)	(1.0)
RAP, mmHg	8.0**	5.0	4.1**	6.4
	(1.0)	(0.5)	(0.7)	(0.9)
PCWP, mmHg	10.8*	7.0	6.6*	8.6
	(1.9)	(1.0)	(1.3)	(1.0)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 4. Mean (SEM) effects of transfer from $HFJV_1$ to IPPV in group 1 patients, and from IPPV to $HFJV_1$ in group 2 patients, on arterial oxygen tension (Pa_{O_2}), cardiac output ($\dot{Q}_t$), total tissue oxygen delivery (flux), left ventricular stroke work index (LVSWI) and stroke index (SI).

	Group 1		Group 2	
	$HFJV_1$	IPPV	IPPV	$HFJV_1$
Pa_{O_2}, kPa	33.4**	41.6	52.8**	46.9
	(5.2)	(5.2)	(4.4)	(3.7)
$\dot{Q}_t$, litres/minute	5.7**	6.7	5.6*	5.2
	(0.3)	(0.3)	(3.0)	(0.2)
Flux, ml/minute	975**	1114	938*	854
	(61)	(71)	(62)	(43)
LVSWI, g m/sq. m	28**	35	35*	30
	(2.4)	(1.7)	(2.6)	(2.5)
SI, ml/sq. m	32**	38	35	33
	(2.1)	(1.7)	(1.6)	(1.5)

* $p < 0.05$; ** $p < 0.01$.

Table 5. Mean (SEM) effects of the gradual application of PEEP following transfer from IPPV to HFJV in group 1 patients, on pulmonary artery pressure (PAP), right atrial pressure (RAP), shunt fraction ($\dot{Q}_s/\dot{Q}_t$) and arterial oxygen tension (Pa_{O_2}).

	IPPV	$HFJV_1$
PAP, mmHg	12.5***	17.5
	(1.1)	(0.9)
RAP, mmHg	3.5***	8.0
	(0.5)	(1.0)
$\dot{Q}_s/\dot{Q}_t$, %	17.4**	20.6
	(2.1)	(2.1)
Pa_{O_2}, kPa	46***	33.4
	(4.9)	(5.2)

** $p < 0.01$; *** $p < 0.001$. Changes in other parameters were not significant.

to increase peak P_{aw} to values comparable to those during IPPV, caused significant increases in mean P_{aw}, PAP, RAP and shunt fraction ($\dot{Q}_s/\dot{Q}_t$), whereas Pa_{O_2} decreased significantly.

Discussion

There is a progressive improvement in the circulation following the withdrawal of cardiopulmonary bypass support, which is maintained throughout the early postoperative period. Thus circulatory changes observed following any alteration in the mode of ventilation during this time might be merely coincidental, i.e. the signs of an improving circulation upon which the possibly trivial haemodynamic consequences of ventilation are superimposed. Examination of the data from patients in both groups 1 and 2 shows that there were no significant differences in heart rate, SAP, PAP, PCWP, $\dot{Q}_t$, SI or flux when values at the beginning of the study are compared with those at the end (i.e. IPPV1 *versus* IPPV2). Such differences as do occur (i.e. in Pa_{O_2} and $\dot{Q}_s/\dot{Q}_t$) are more probably the result of changing the method of delivery of controlled ventilation during the study, rather than the consequences of a changing haemodynamic state. Similarly, we believe that the haemodynamic changes seen during this study are the result of the effects of HFJV, with and without added PEEP, and are not simply the observation of a post-bypass circulation that improved with time.

The HFJV settings used in this study reflect our practice and clinical experience with the technique. There is evidence that respiratory rates greater than 150 breaths/minute may have adverse haemodynamic effects,[5] and that inspiratory ratios greater than 30% of total inspiratory time may cause alveolar overdistension.[6]

The data in Figs 3–8 confirm the assumption that all patients had good left ventricular function. $\dot{Q}_t$ and SI were well maintained, and PCWP and PAP were low throughout the study. Indeed, it should be emphasised that all of these patients had an uneventful postoperative course.

The points of particular interest relate to the application of additional PEEP to HFJV, and the relationships between mean and peak airway pressures and cardiorespiratory parameters in patients during recovery from ACBG surgery.

The transfer of patients from IPPV to HFJV with no added PEEP, was associated with an

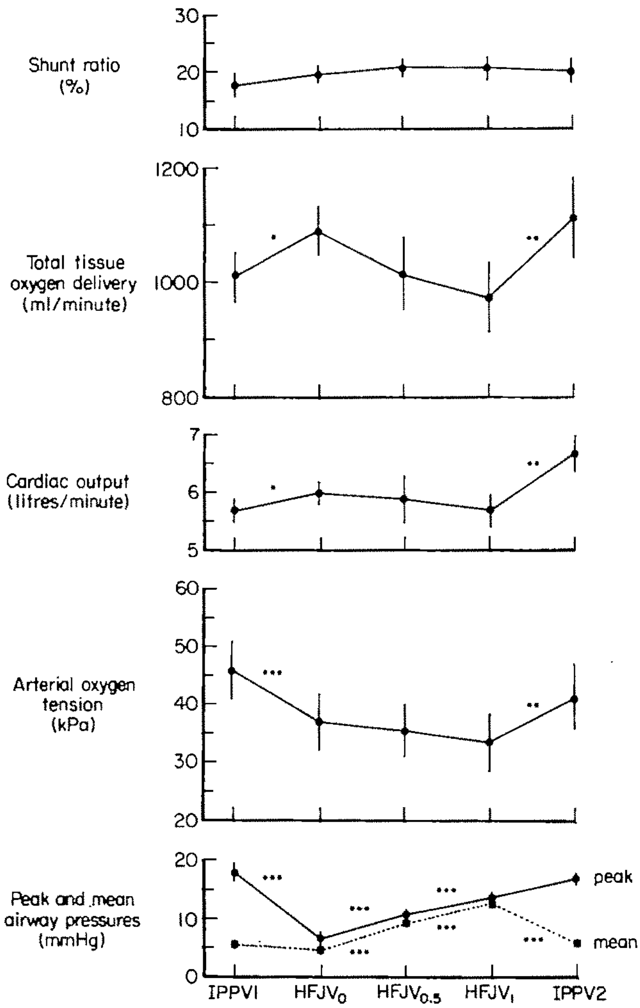

Fig. 4. Effects of transfer in group 1 patients from IPPV to HFJV with gradual application of up to 1 kPa PEEP. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

immediate and significant decrease in $P\text{a}O_2$. Peak P_{aw} was also significantly lower but mean P_{aw} remained essentially unchanged. However, there was an immediate and significant increase in $\dot{Q}_t$, and flux actually increased. The mechanism of the increase in $\dot{Q}_t$ is unclear but, since SI and LVSWI were unchanged, the increase in $\dot{Q}_t$ was the result of a slight increase in heart rate (Figs 3–5). Thus, in this group of patients, the decrease in $P\text{a}O_2$ associated with transfer from IPPV to HFJV was more than compensated for by an increase in $\dot{Q}_t$, resulting in a significant improvement in tissue oxygen delivery.

Nevertheless, a decrease in $P\text{a}O_2$ of nearly 20% (as occurred in group 1 patients) could be alarming under certain conditions. Extrapolating from experience with IPPV, it appears reasonable to attempt to minimise this fall in $P\text{a}O_2$ by the controlled application of PEEP. The application of PEEP during IPPV may produce both beneficial and detrimental effects. The recruitment of atelectatic areas for gas exchange is of benefit; functional residual capacity and $P\text{a}O_2$ are thus increased. However, overdistension of alveoli may cause decreased compliance and pulmonary barotrauma; venous return may also be impeded, thereby reducing $\dot{Q}_t$.[7] Thus there is a theoretical optimum level of PEEP for each

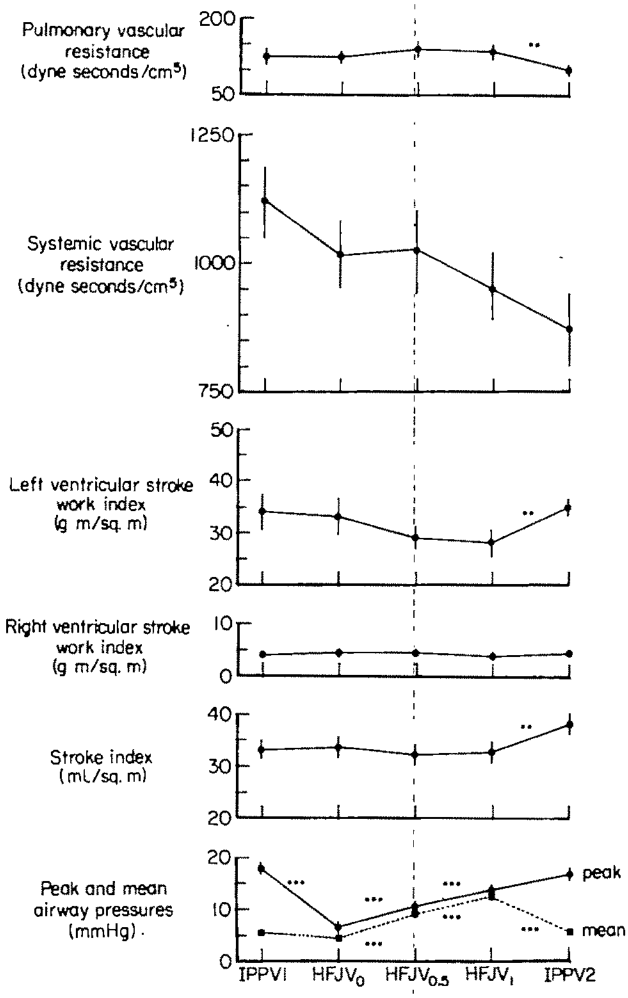

Fig. 5. Effects of transfer in group 1 patients from IPPV to HFJV with gradual application of up to 1 kPa PEEP: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

patient at which the balance between improved gas exchange and decreased haemodynamic function results in the highest flux. HFJV at the respiratory rates used causes a certain amount of inherent PEEP in the lungs (0.1–0.4 kPa with the system used in this study).

High levels of PEEP are associated with increased airway pressures throughout the respiratory cycle. At $HFJV_1$, patients in groups 1 and 2 appeared to be at little or no added risk from barotrauma in comparison to IPPV, since peak P_{aw} was similar. Mean P_{aw} increased significantly which, theoretically, improves recruitment of atelectatic areas for gas exchange. However, the effects of the higher airway pressure on cardiorespiratory variables were disturbing.

Pa_{O_2} decreased following direct transfer from IPPV to $HFJV_1$ in patients in group 2. There were also immediate and significant increases in PAP, RAP and PCWP, and a significant decrease in $\dot{Q}_t$. Thus, tissue oxygen delivery was reduced significantly. These changes were mirrored almost exactly upon transfer from $HFJV_1$ to IPPV in group 1: PAP, RAP and PCWP decreased, and $\dot{Q}_t$ and flux increased. LVSWI and SI were significantly less during $HFJV_1$ when compared to IPPV (Table 4). Thus it would appear that the

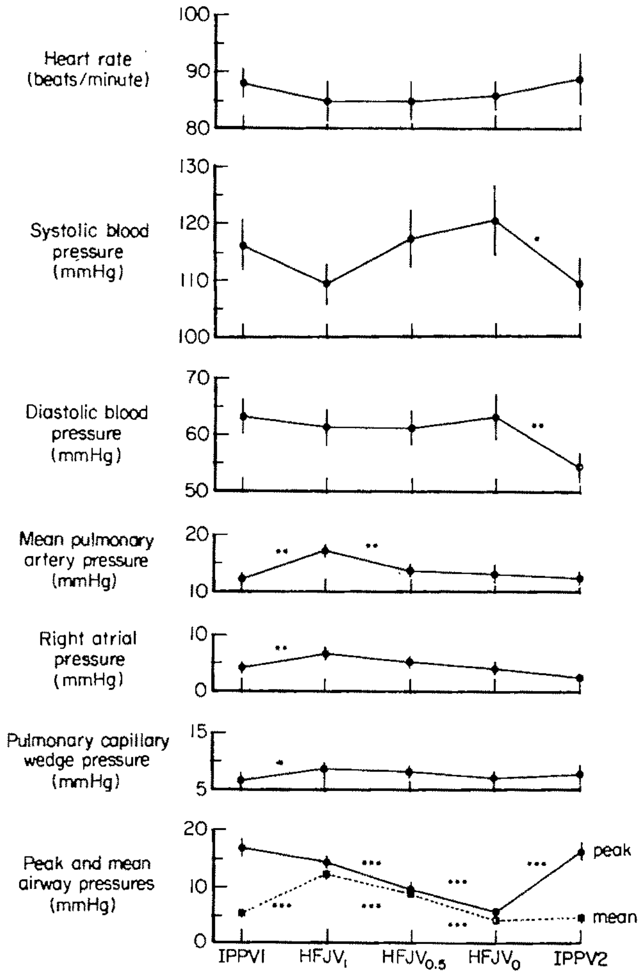

Fig. 6. Effects of transfer in group 2 patients from IPPV to HFJV and gradual reduction from 1 kPa PEEP. *p < 0.05; **p < 0.01; ***p < 0.001.

sudden transfer of patients from IPPV to $HFJV_1$ did not prevent the decrease in Pa_{O_2} and, furthermore, had adverse circulatory effects.

It might be that the gradual introduction of an equivalent amount of PEEP would be better tolerated. We were able to evaluate this by comparison between IPPV and $HFJV_1$ in group 1 patients in whom the additional PEEP was introduced gradually. The changes were not as marked as those described above, but there was still a significant decrease in Pa_{O_2}, and significant increases in PAP, RAP and $\dot{Q}_s/\dot{Q}_t$.

Comparison of IPPV with $HFJV_{0.5}$ in both groups highlighted a number of changes, but no identifiable pattern. Mean P_{aw} was greater, and peak P_{aw} was less, than those seen during IPPV. However, other changes, including changes in Pa_{O_2} and $\dot{Q}_t$, seemed to be influenced most by the preceding step, i.e. whether it was $HFJV_0$ or $HFJV_1$. It would appear from our data that the reduction in Pa_{O_2} on instituting $HFJV_0$ cannot be prevented by the later application of PEEP.

The decrease in Pa_{O_2} reported here during $HFJV_0$ is in agreement with our own previous clinical observations and those of others.[8] However, our experience is that these changes are usually short-lived. The reason why this effect is apparently self-limiting is not clear but, possibly, a progressively more even distribution of gas during HFJV, and vasoconstriction within

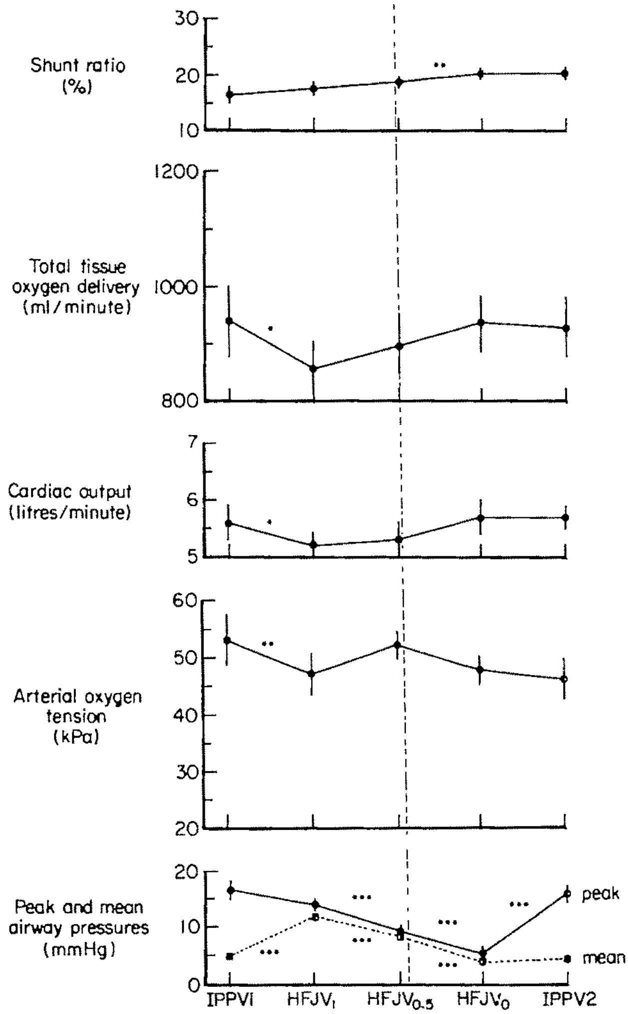

Fig. 7. Effects of transfer in group 2 patients from IPPV to HFJV and gradual reduction from 1 kPa PEEP. *p < 0.05; **p < 0.01; ***p < 0.001.

hypoxic atelectatic areas of the lung, may be implicated. The effects of $HFJV_0$ on cardiac output reported in the literature are conflicting.[1,9–14] Our observations suggest that large increases in mean P_{aw} are related inversely to changes in $\dot{Q}_t$ and, similarly, that when mean P_{aw} decreases significantly, $\dot{Q}_t$ is increased. This would be in agreement with other studies,[10] particularly if lung compliance is reduced and mean P_{aw} is elevated, for example in adult respiratory distress syndrome.[14] However, mean P_{aw} was low even during IPPV in our series of patients, and therefore the beneficial effect on $\dot{Q}_t$ of transfer to $HFJV_0$ from IPPV, was minimal.

The reduction in Pa_{O_2} on changing from IPPV to $HFJV_0$ in this study was significant. However, the effect on total tissue oxygen delivery may have been influenced by the fact that the study was carried out with an inspired oxygen concentration of 100%; at the high oxygen tensions observed during this study there would be very small changes in oxygen saturation, due to the shape of the oxygen dissociation curve.

Our experience that HFJV is well tolerated during recovery from ACBG surgery is in agreement with that of others who have studied patients after cardiac surgery.[15] We have found

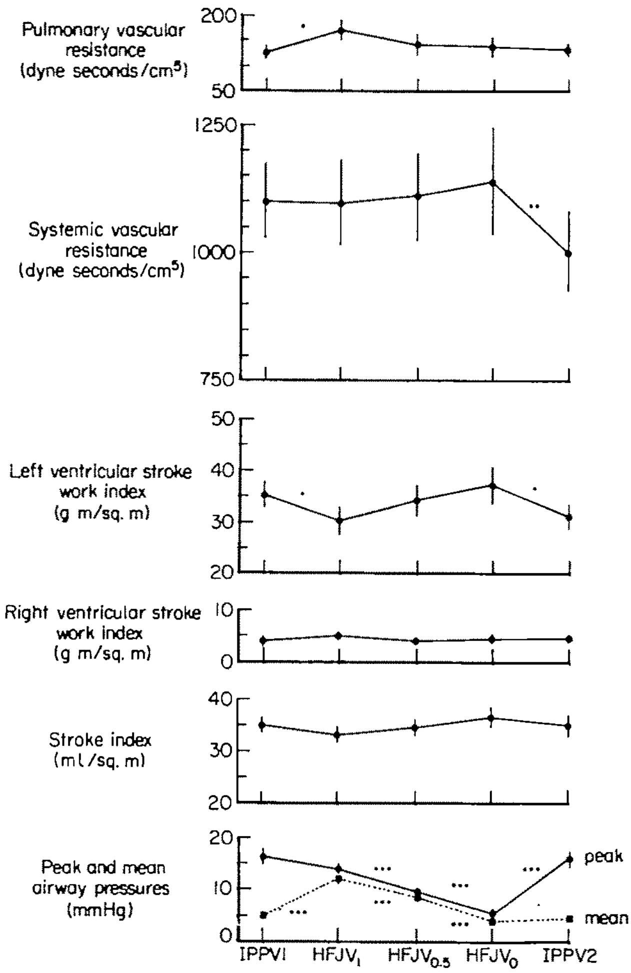

Fig. 8. Effects of transfer in group 2 patients from IPPV to HFJV and gradual reduction from 1 kPa PEEP. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

the valveless patient system to be useful for weaning patients from the ventilator. Respiratory pattern is organised and productive, possibly as a result of reduced phrenic nerve activity caused by the inherent PEEP within the system.[16] There is evidence that changes in $Pa\text{O}_2$ during HFJV relate consistently to changes in mean P_{aw},[17,18] although this has been disputed.[15] We were unable to correlate changes in mean P_{aw} with changes in $Pa\text{O}_2$ during this study. We were impressed by the reduction in peak P_{aw} during HFJV$_0$ in comparison with IPPV. This has been reported elsewhere with HFJV systems[19,20] and may be of greater importance in cases of severe lung disease.[21–23] The advantages of a reduction in peak P_{aw} in the group of patients reported here remain unclear.

In conclusion, the haemodynamic effects of HFJV without added PEEP were comparable to those of IPPV in both group of patients in this study. HFJV without added PEEP may be useful in patients in whom it is important to minimise P_{aw}. The addition of further PEEP sufficient to elevate P_{aw} to values comparable to those seen during IPPV, caused a significant increase in mean P_{aw}, with consequent haemodynamic impairment. However, the decreases in $Pa\text{O}_2$

and flux were not prevented by this level of additional PEEP. We were unable to identify any advantage in the addition of further PEEP to HFJV in this group of patients.

Acknowledgments

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Bradycardia during intra-abdominal surgery

Modification by pre-operative anticholinergic agents

D. M. COVENTRY, I. McMENEMIN AND S. LAWRIE

Summary

The aim of the present study was to examine, in a double-blind, randomised manner, the effects of glycopyrronium 0.005 mg/kg, atropine 0.01 mg/kg or a placebo (normal saline) on the frequency of bradycardia in 92 patients scheduled for major abdominal or gynaecological surgery. All patients received fentanyl, halothane and vecuronium. The frequency of bradycardia in the group that received saline was 18%. No cases occurred in either anticholinergic group. Mean heart rates intra-operatively were not significantly different between the atropine and glycopyrronium groups. It is suggested that the routine use of pre-operative anticholinergic agents should be considered when a similar anaesthetic technique is employed.

Key words

Premedication; atropine, glycopyrronium.
Heart; bradycardia.

Increasing concern has been expressed over bradycardia which occurs in association with the newer muscle relaxants, atracurium and vecuronium.[1–8] Neither agent has intrinsic cardiovascular effects,[9–13] so the bradycardia is attributed either to the pharmacological properties of other agents used, such as fentanyl or halothane, or to physiological reflexes associated with peritoneal traction or other intra-abdominal manipulations. Using a double-blind, randomised technique, we compared intravenous atropine and glycopyrronium with respect to alteration in heart rate and rhythm, as well as efficacy in prevention of bradycardia during intra-abdominal surgery. An anaesthetic technique that employed vecuronium, fentanyl and halothane was used.

Methods

Ninety-two patients scheduled to undergo elective major intra-abdominal or gynaecological surgery were studied. All were under 65 years of age and of ASA grade 1 or 2. Patients with known cardiovascular disease, or those taking any medication known to alter heart rate or rhythm, were excluded, as were those with potential intubation problems or at risk of regurgitation. Informed patient consent was obtained. All were premedicated with lorazepam 2.5–4 mg orally 2 and 3 hours before operation.

Intravenous access was established on arrival at the anaesthetic room, continuous monitoring of the electrocardiograph (ECG) was commenced (Simonsen and Weil Diascope, DS 521)

D.M. Coventry,* MB, ChB, FFARCS, I. McMenemin,† MB, ChB, FFARCS, S. Lawrie, MB, ChB, FFARCS, Registrars, Department of Anaesthesia, Victoria Infirmary, Langside, Glasgow G42 9TY.
* Now Senior Registrar, Department of Anaesthesia, Western Infirmary, Glasgow G11.
† Now Research Fellow, University Department of Anaesthesia, Royal Infirmary, Glasgow.

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and arterial pressure recorded indirectly (Sentry ASD 400, Automated Screening Devices Inc.). Three minutes before induction the patient received either atropine 0.01 mg/kg, glycopyrronium 0.005 mg/kg or normal saline (control) in a volume of 0.025 ml/kg intravenously. The ampoules were prepared in a randomised and double-blind manner.

Anaesthesia was induced with intravenous administration of fentanyl 3 μg/kg followed by thiopentone 5 mg/kg, and muscle relaxation achieved with vecuronium 0.1 mg/kg. The patient's lungs were ventilated with 70% nitrous oxide in oxygen by facemask for 2 minutes before tracheal intubation was performed. Thereafter halothane 0.5% was added, ventilation was controlled using a Manley Pulmovent (minute volume 100 ml/kg) and 10 minutes allowed to elapse prior to surgical incision. Depth of anaesthesia was then altered, if required, by adjusting the inspired halothane concentration.

Recordings of heart rate and arterial pressure were made at 2-minute intervals before incision and thereafter at 5-minute intervals for a further 20 minutes. The ECG was monitored throughout for any changes of cardiac rhythm. The occurrence of a heart rate below 50 beats/minute was defined as a bradycardia and treated using 0.2 mg increments of atropine. Subsequent recordings for the trial were then discontinued and details of the precipitating surgical stimulus, if any, recorded.

The heart rates and arterial pressures in each group of patients were analysed using Student's *t*-test. The incidence of bradycardia in each group was analysed using Fisher's exact test.

Results

The mean age and weight of the patients were similar in all three groups (Table 1). There was a larger total number of females in the study but all three groups were considered comparable.

Mean heart rates, as shown in Fig. 1, were not significantly different before administration of

Table 1. Patient data.

	Control	Atropine	Glycopyrronium
Number of patients	28	28	36
Mean age (SEM), years	42 (2)	42 (2)	42 (2)
Mean weight (SEM), kg	63 (1)	63 (2)	64 (2)
Males	5	8	9
Females	23	20	27

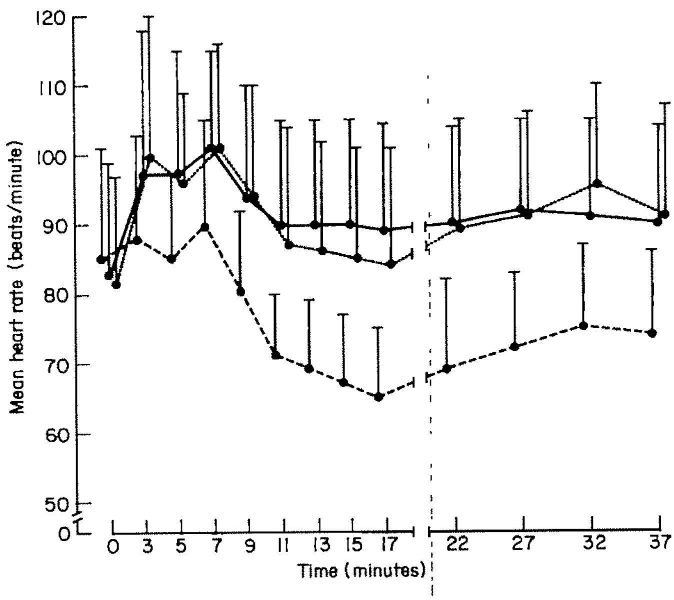

Fig. 1. Mean (SD) intra-operative heart rate following the administration of atropine 0.01 mg/kg (· · · ·), glycopyrronium 0.005 mg/kg (——) and saline (– – – – –). The anticholinergic preparation was given at time 0. Induction is at 3 minutes and incision at 17 minutes.

Table 2. Occurrence of dysrhythmia and bradycardia.

Drug	Dysrhythmia	Bradycardia
Glycopyrronium (n = 36)	7 (20%)	0 (0%)
Atropine (n = 28)	3 (11%)	0 (0%)
Control (n = 28)	6 (21%)	5 (18%)

the anticholinergic preparation (0 minutes). Serial heart rates recorded between time of induction at 3 minutes and 37 minutes, demonstrate a significantly faster heart rate in the groups that received anticholinergic agents ($p < 0.05$) but no statistical difference between the atropine and glycopyrronium groups. Both agents were equally effective in preventing the occurrence of intra-operative bradycardia (Table 2). Compared with the other two groups, there was a significant incidence of bradycardia in the control group ($p < 0.005$). Of the five cases of bradycardia (Table 3), two were particularly severe; an asystolic cardiac arrest during an otherwise routine hysterectomy in a fit 37-year-old patient, and an idioventricular rhythm of 20 beats/minute that occurred in a 64-year-old patient undergoing cholecystectomy. Both were successfully resuscitated without any further complications, although the former patient required external cardiac massage for 20 seconds before return of a spontaneous rhythm. No bradycardia occurred in any patient before surgical stimulation.

Heart rates greater than 120 beats/minute occurred only in the atropine and glycopyrronium groups (Table 4) but there was no statistically significant difference between them. There was no significant difference in the number of dysrhythmias that occurred in any of the three groups (Table 2). There were no differences in arterial pressures between the three groups.

Discussion

The occurrence of bradycardia as a result of severe cholinergic challenges, such as repeated suxamethonium administration or during ophthalmic surgery, is well documented.[14–17] This has prompted many anaesthetists to employ an anticholinergic preparation routinely as part of their anaesthetic technique. The results of this study show that a significant number of patients who undergo intra-abdominal or major gynaecological surgery are at risk of developing severe, possibly life-threatening bradycardia when an anaesthetic technique which employs halothane, fentanyl and vecuronium is used. It would seem that pharmacological interactions alone are unlikely to be responsible, since none of these occurred in the 10-minute study period before incision. Fentanyl and other opioids have been shown to cause significant reduction in heart rate,[18,19] possibly by reduction in sympathetic drive or by increase in vagal tone by direct central stimulation of the vagal nucleus.[20] Halothane is known to decrease heart rate by reduction of sinus node transmission and atrioventricular conduction.[21] Conversely, vecuronium has been shown in many studies to have no significant effect on heart rate,[9–13] although reports have appeared of bradycardia in association with its use during intra-abdominal surgery.

All the incidents of bradycardia in this study occurred during surgical stimulation or retraction (Table 3), which suggests that haemodynamic changes occur in response to intra-abdominal manipulations. A recent study by Seltzer and colleagues[22] reported a significant increase in heart rate accompanied by a reduction in arterial pressure and increase in cardiac output, during standardised traction on the abdominal mesentery. Three patients out of 20, however, exhibited a decrease in heart rate, although no severe bradycardia was reported. The

Table 3. Details of patients who exhibited bradycardia.

Procedure	Age	Sex	Lowest heart rate (beats/minute)	Surgical stimulus
Cholecystectomy	64	F	20	Traction around porta hepatis
Abdominal hysterectomy	37	F	0	Insertion of pack into pelvis
Ovarian cystectomy	17	F	45	Peritoneal traction
Abdominal hysterectomy	44	F	41	Insertion of pack into pelvis
Ovarian cystectomy	44	F	43	Cervical dilatation

Table 4. Occurrence of tachycardia 3 minutes after administration of drug.

Drug	Tachycardia >100 beats/minute	Tachycardia >120 beats/minute
Glycopyrronium (n = 36)	13 (36%)	6 (17%)
Atropine (n = 28)	14 (50%)	3 (11%)
Control (n = 28)	6 (21%)	0 (0%)

nature of the reflex arc, if one exists, remains unclear. Afferent impulses may ascend via sympathetic, phrenic, vagus, sacral parasympathetic or possibly intercostal nerves, and result in an increase or inhibition of sympathetic activity, or an increase in vagal tone. The response to abdominal mesenteric traction is therefore not universal, and may also vary according to the area or organ stimulated.

Both atropine and glycopyrronium given intravenously before induction proved equally effective in protection of the patient from bradycardia, although at the expense of unwanted tachycardia in some patients in both groups. Glycopyrronium 0.2 mg intravenously has been shown to have minimal effects on heart rate and rhythm[23] but comparable doses of atropine and glycopyrronium appear to differ only in their rate of onset;[24] glycopyrronium takes around one minute longer to act. This feature is particularly valuable in the reversal of neuromuscular blockade with neostigmine,[25] since the initial tachycardia seen with atropine is avoided. In the preoperative situation, however, the only theoretical benefit of glycopyrronium over atropine is its longer duration of action.[26] Glycopyrronium has been shown to cause a lesser increase in heart rate than atropine when given intramuscularly as an antisialogogue,[27] but this route of administration has not been shown to offer protection against a severe cholinergic challenge.[16]

An initial tachycardia in otherwise fit individuals is unlikely to be of significant clinical importance when balanced against the life-threatening bradycardia which may occur, particularly in the younger age group where vagal reflexes are considered to be more active. In the older patient and those with ischaemic heart disease, impaired myocardial perfusion as a result of a tachycardia may present a more significant problem than a potential bradycardia. Therefore, the use of an anticholinergic agent only if and when required, seems more appropriate.

In conclusion, the incidence, severity and unpredictability of bradycardia that occurs with the described technique, are of sufficient magnitude to merit consideration of the routine use of an anticholinergic agent in the majority of patients who present for major intra-abdominal surgery. There appears to be no additional benefit conferred by the use of glycopyrronium rather than atropine in this situation.

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Controlled release morphine tablets: a double-blind trial in patients with advanced cancer

G. W. HANKS, R. G. TWYCROSS AND J. M. BLISS

Summary

Eighteen of 27 patients with pain due to advanced cancer, completed a randomised crossover comparison of 4-hourly aqueous morphine sulphate and twice daily controlled release morphine tablets. There was no difference between the two regimens in analgesic efficacy or adverse effects, but there was an apparent improvement in quality of sleep on the controlled release tablets. After completion of the study, 17 patients continued with the latter medication for periods that ranged from 2 days to 94 weeks (median 6.5 weeks). Controlled release morphine tablets given twice daily provide a simpler and more convenient treatment regimen than a 4-hourly opioid for patients with cancer pain, once they have been stabilised.

Key words

Analgesics, narcotic; morphine, sustained release morphine.
Pain; chronic.

Controlled release morphine tablets (MST Continus) are now widely used in the treatment of cancer pain and, to a lesser extent, peri-operatively.[1] There is, however, a paucity of controlled clinical trial data on the use of MST in cancer patients. This has led to confusion about the duration of analgesic activity and the relative potency of MST.

In an earlier single-dose study in post dental surgery patients, we found that MST does produce sustained plasma concentrations of morphine.[2] This had been shown earlier in healthy volunteers[3] and has been confirmed subsequently in patients with cancer.[4] There are no published data on the pharmacokinetics of repeated doses of MST. An investigation of the bio-availability of this formulation[5] is difficult to interpret because of doubts about the specificity of the assay employed.[6,7] Thus, there are at present insufficient data on which to base recommendations about the optimum dose regimen for MST in cancer patients and the equivalent dose in relation to morphine sulphate in solution and other opioids.

We report here the results of a randomised double-blind crossover comparison of MST and

G.W. Hanks,* BSc, MRCP, Research Fellow, R.G. Twycross, DM, FRCP, Consultant Physician, Sir Michael Sobell House, Churchill Hospital, Headington, Oxford OX3 7LJ, J.M. Bliss, MSc, Statistician, Division of Epidemiology, Institute of Cancer Research, Clifton Avenue, Belmont, Sutton, Surrey SM2 5PX.

* Present appointment: Consultant Physician and Honorary Senior Lecturer, Royal Marsden Hospital and Institute of Cancer Research, London.

Correspondence should be addressed to Dr G.W. Hanks, Royal Marsden Hospital, Fulham Road, London SW3 6JJ.

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aqueous morphine sulphate in patients with chronic cancer pain. An interim report of this study has been published previously.[8]

Methods

Patients with advanced cancer admitted to a hospital-based continuing care unit were eligible for the study if they had pain which was controlled with 4-hourly oral morphine sulphate in aqueous solution. Only patients who had received the same dose of morphine for at least 7 days were asked to participate in the trial. Patients who were too ill or confused, or patients whose pain was not stable, were not studied. Full explanation of the aims of the study and of the procedures involved, was given to all patients before consent to participate was obtained. The study protocol was approved by the Ethics Committee of the Oxfordshire Area Health Authority.

Patients who fulfilled the entry criteria and who gave consent to take part in the study were randomly assigned to treatment with MST tablets given twice a day (10:00 and 22:00 hours) or to continue with 4-hourly aqueous morphine (06:00, 10:00, 14:00, 18:00, 22:00 hours and, for some patients, 02:00 hours). After 2 days, treatment was switched to the alternative formulation and continued for a further 2 days. A double dummy technique was used: all patients received tablets twice daily (active or placebo) and solution every 4 hours (active or placebo) for the duration of the study period. In either case the same total daily dose of morphine was maintained.

Self-assessments of pain, alertness, nausea and mood on 10-cm visual analogue scales (VAS) were completed twice daily under the supervision of an experienced research nurse, just before the 10:00 hours medication and 6 hours later. An assessment of sleep was included each morning and of appetite, each afternoon. In addition, nurse and patient recorded scores on a global five-point pain scale at the same time as the VAS ratings (0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; 4, excruciating pain).

The ratings and VAS scores for days 1 and 2 were compared with those for days 2 and 4. At the end of the study period, patient and nurse noted their preference for the first or second treatment phase. Patients for whom there appeared to be no difference between the treatment periods, continued to use MST after they had completed the study.

Statistical methods. Changes between the baseline level and final readings for each treatment phase were calculated for each VAS rating. For those patients who completed the trial the results of the various assessments were analysed using standard crossover-design nonparametric techniques. The changes from baseline level were compared for the two treatment regimens using the Mann–Whitney U test.

Results

Thirty-six patients gave consent to participate in the study and 27 actually entered (consent was obtained on a Friday, with a view to starting the study the following Monday). The nine patients who gave consent to participate but were not entered, were not studied either because their pain did not remain controlled on the same dose of morphine, or because their general condition had deteriorated. Eighteen patients completed the study. These comprised seven males aged 59–78 years (mean 72 years) with carcinoma of the colon (2), stomach, rectum and prostate, one with an unknown primary and one patient with non-malignant disease (peroneal muscular atrophy), and 11 females aged 53–82 years (mean 68 years) with carcinoma of the breast (6), rectum, kidney and urethra, one with a leiomyosarcoma and one with myeloma.

Of the nine patients who entered the study but were withdrawn before completion, six were males aged 54–80 years (mean 69 years) with carcinoma of the stomach, rectum, bronchus, tonsil, pancreas and one patient with an unknown primary, and three were females aged 51–71 years (mean 63 years) with carcinoma of the breast (2) and bronchus. Seven patients were withdrawn whilst they received aqueous morphine, four because of a general deterioration in their condition, two because of a disinclination to continue in the study, and one because of breakthrough pain. Two patients were withdrawn during the MST phase; one became extremely drowsy on the second MST day (on a dose of 100 mg twice daily) and the other started to vomit because of subacute intestinal obstruction. The patients who were withdrawn did not share any particular characteristics and there was no pattern of withdrawal which is likely to be related to the analgesic regimen.

Table 1. Results of visual analogue scale scores: values expressed as mean (SE).

	Pain*	Alertness*	Nausea*	Mood†	Sleep†	Appetite†
Aqueous morphine						
Initial	86.1 (2.8)	51.7 (8.0)	84.8 (3.6)	14.9 (4.6)	16.3 (4.3)	19.1 (6.5)
Final	82.4 (4.8)	81.7 (4.3)	87.8 (3.7)	18.5 (5.4)	22.3 (4.5)	28.8 (8.4)
95% CI (for change)	−7.1–+14.4	−46.3–−13.6	−11.5–+5.5	−10.2–+3.1	−15.8–+3.7	−24.1–+4.7
Median change	0.0	−20.5	−2.5	−0.5	−2.0	0.0
Range	−51.0–+60.0	−96.0–+15.0	−52.0–+35.0	−26.0–+19.0	−47.0–+38.0	−84.0–+22.0
MST						
Initial	80.2 (5.0)	78.8 (4.1)	86.9 (3.1)	15.2 (4.2)	28.6 (6.7)	24.9 (7.2)
Final	75.3 (7.2)	75.2 (6.0)	85.8 (5.1)	14.5 (4.8)	13.6 (3.1)	32.0 (8.0)
95% CI (for change)	−10.0–+19.6	−8.1–+15.3	−9.2–+11.5	−4.1–+5.6	3.3–26.8	−17.7–+3.4
Median change	0.0	−0.5	0.5	1.00	6.5	0.0
Range	−55.0–+71.0	−47.0–+58.0	−51.0–+58.0	−29.0–+19.0	−17.0–+81.0	−72.0–+10.0
p	0.948	0.007	0.339	0.266	0.017	0.938

* 100 = no pain, fully alert, no nausea (i.e. positive change in condition, results in a negative change value).
† 0 = not at all depressed, best possible night's sleep, normal appetite (i.e. positive change in condition, results in a positive change value).
CI, confidence interval.

When the changes for the two groups were compared, no evidence of a period (order) or carryover effect was found in any of the VAS ratings except for a possible carryover effect in the ratings for nausea. The data were therefore combined and examined for a difference between the two treatment regimens (i.e. irrespective of order of treatment received).

The results of the VAS assessments for patients who completed the study are shown in Table 1. Details of initial and final readings for each treatment phase are given, together with 95% confidence intervals for the mean change in ratings over that treatment phase. In general there was only a small and nonsignificant change from baseline values, with no difference between MST and aqueous morphine in the ratings for pain, nausea, appetite and mood.

There was a significant difference between the groups with respect to ratings of alertness and sleep. Patients who received aqueous morphine showed an improvement in alertness. The baseline value here was, however, unusually low, so that the apparent improvement may be artefact. In contrast, when patients received MST there was an improvement in the quality of sleep, with no change in this rating during the aqueous morphine phase.

The results of the global assessments are shown in Table 2. Two-thirds of the patients had no pain during both phases.

No specific adverse effects were encountered apart from drowsiness in one patient (noted above). When asked which treatment period was preferred overall, 14 patients expressed no preference, three preferred the aqueous morphine phase and one the MST phase. The research nurse expressed no preference in 13 patients, in four the aqueous morphine phase and in one patient, the MST phase.

Table 2. Results of global assessment. Cross-tabulation of values at the end of each treatment period.

Aqueous morphine scores	MST scores 0	1	2	3	Total
0	12	0	0	0	12
1	0	2	1	0	3
2	0	0	1	0	1
3	0	0	1	1	2
Total	12	2	3	1	18

Only two entries are off the leading diagonal, i.e. involve change across treatments.

The exceptionally high dropout rate is worrying and we carried out a further analysis to examine whether the withdrawal of patients was independent of the treatment received in the trial. The first treatment period was considered alone, including those patients subsequently withdrawn, to see whether these patients had results comparable to those who completed the study.

Analysis of these data using two-sample t-tests gave results very similar to those obtained from analysis of the full trial data. Again, a signifi-

cant difference between the treatment groups ($p < 0.01$) was observed in alertness and, once more, this is explained by the very low initial ratings in the aqueous morphine group. Otherwise there was no difference between MST and aqueous morphine in the ratings for pain, nausea, appetite and mood.

Seventeen of the 18 patients who completed the study were subsequently prescribed MST and continued with it for periods that ranged from 2 days to 94 weeks (median 6.5 weeks). Doses used ranged from 20 mg twice daily to 200 mg twice daily; one patient (who received 180 mg/day) required a thrice daily dosing. The median dose was 90 mg/day. The eighteenth patient was changed back to aqueous morphine because she had a fall on the last day of the study, with a resultant increase in her pain which became progressively more severe over the ensuing weeks.

Discussion

The patients who entered this study were stable clinically and were at steady state with their 4-hourly aqueous morphine. Pain was controlled equally well on twice daily MST and remained so in all cases until they entered the terminal phase of their illness.

The apparent improvement in alertness during the aqueous morphine phase is inconclusive because of the low baseline value. All of the patients in the study had received a stable dose of aqueous morphine for at least 7 days, and no change in levels of alertness would normally be expected. The more relevant finding is that there was no deterioration in alertness during treatment with MST.

The difference between treatments with respect to quality of sleep may be more important, and may be a real benefit of the steady plasma concentrations produced by MST. This difference in sleep ratings cannot be explained merely by the avoidance of a middle of the night dose of aqueous morphine. Only three of the 18 patients who completed the study were awakened at night for a 02:00 hours dose during their aqueous morphine phase; the rest had an increased or double dose at the end of the day.

In this study we used a milligram-for-milligram conversion ratio when we changed from aqueous morphine to MST. There have been suggestions that MST is more bioavailable than aqueous morphine and, therefore, relatively more potent. Our study data and subsequent experience do not support this contention.

One patient experienced breakthrough pain before each dose when given MST twice daily, but his pain was well controlled on an 8-hourly regimen that used the same total daily dose. Since this study was undertaken we have treated several hundred patients with MST. The great majority have been pain-controlled with twice daily administration of the tablets. Thus the routine use of MST in a three or four times a day regimen is ill-founded and unnecessary.

MST has important advantages for patients who require long-term morphine therapy, whose overall drug treatment can be contained in a twice or three times daily regimen. On the other hand, we consider that MST should not be used to titrate dosage in patients when they start on oral opioids. It takes up to 4 hours for peak plasma concentrations of morphine to be achieved with MST[2] compared with 1.5–2 hours after aqueous morphine, and the onset of significant analgesic effect will be correspondingly delayed. Aqueous morphine is thus a better formulation to use when a patient's dose requirements are determined. For the same reasons, MST is not appropriate for administration on a 'when required' basis to treat breakthrough pain. Used correctly, however, MST can simplify treatment regimens for cancer patients with chronic pain.

This study also illustrates one of the major difficulties of conducting clinical trials in a continuing care unit. The dropout rate was 50%, half of whom were withdrawn between the time when they gave consent to participate and when they should have entered the study. Clearly this is a potential source of bias[9] and, in future studies, we would obtain consent immediately before patients were entered into a study. Our analysis of the data which includes the withdrawals does indicate that, in this case, our conclusions are valid in spite of the high withdrawal rate.

Acknowledgments

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Anaesthesia, 1987, Volume 42, pages 845–849

Comparison of two regional techniques for postoperative analgesia in children following herniotomy and orchidopexy

G. D. CROSS AND R. F. BARRETT

Summary

This study compares the quality and duration of analgesia in two groups of patients aged between 1 and 13 years who received either caudal anaesthesia with plain bupivacaine 0.25% or an iliohypogastric and inguinal nerve block combined with skin infiltration using bupivacaine 0.25% with adrenaline 1:200 000. The results indicate no significant difference in the duration or quality of the analgesia provided by the two techniques. There was no difference in the incidence of vomiting or the time of first micturition between the two groups.

Key words

Pain; postoperative.
Anaesthetic techniques, regional; caudal, iliohypogastric and ilio-inguinal block.

Conventional postoperative analgesia for paediatric surgery involves the administration of either opioid injections or oral analgesics. However, repeated intramuscular injections are unpopular with children and also often cause nausea, vomiting and unwanted sedation; furthermore, the administration of such injections requires trained nursing staff and hospitalisation prevents early discharge home. The selective use of regional anaesthetics administered during general anaesthesia is able to provide pain-free recovery which, with the use of the longer-acting local anaesthetic agents, can last well into the postoperative period and reduce the need for either conventional intramuscular injections or oral analgesics.

Both caudal anaesthesia and an iliohypogastric and ilio-inguinal nerve block using plain bupivacaine 0.25% have been used to provide postoperative analgesia in children who undergo orchidopexy.[1] In the present study, caudal anaesthesia using plain bupivacaine 0.25% was compared with an iliohypogastric and ilio-inguinal nerve block augmented by skin infiltration of the incisional site using bupivacaine with adrenaline. The investigation monitored the duration and quality of the postoperative analgesia provided by the two techniques, following herniotomy and orchidopexy in children.

Method

Forty-one patients between the ages of 1 and 13 years about to undergo either herniotomy or orchidopexy, were randomly allocated to receive either an iliohypogastric and ilio-inguinal nerve block with skin infiltration, or caudal anaesthesia. Patients with spinal cord defects, bleeding diathesis or infection at the site of injection were not studied. The children were premedicated with papaveretum 0.3 mg/kg and hyoscine 0.006 mg/kg given one hour pre-operatively. Anaes-

G.D. Cross, FFARCS, Registrar, R.F. Barrett, FFARCS, Consultant, Department of Anaesthesia, Odstock Hospital, Salisbury, Wiltshire SP2 8BJ.

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thesia was induced either by intravenous thiopentone 4 mg/kg or by inhalation of nitrous oxide, oxygen and halothane, which was used in all cases to maintain anaesthesia. All the local anaesthetics were administered after the induction of general anaesthesia.

The caudal group (group A) received plain bupivacaine 1.0 ml/kg for herniotomy and 1.25 ml/kg for orchidopexy.[2] When the determined volume was less than 20 ml, 0.25% bupivacaine was used but the concentration was reduced to 0.19% bupivacaine for volumes between 20 ml and the maximum of 30 ml.

The iliohypogastric and ilio-inguinal nerve blocks combined with skin infiltration group (group B) received the volume equivalent of 2 mg/kg 0.25% bupivacaine with adrenaline 1:200 000. The designated volume of bupivacaine was used to a maximum of 20 ml for a unilateral block or divided equally between the two sides for a bilateral block to a maximum of 40 ml. For each regional technique one half of the designated volume was administered in a fan-shaped distribution close to the anterior superior iliac spine, to achieve a conduction block of the ilio-inguinal and iliohypogastric nerves. The remaining half of the solution was injected subcutaneously into the proposed incisional site on the lower abdomen; 1–2 ml of this volume were reserved for the incisional site on the scrotum in patients who were to have orchidopexy. The time taken to completion of the local anaesthetic procedure was recorded.

Postoperatively the patients were allowed to recover with minimal disturbance and the time to regaining consciousness, the first micturition and the time of any vomiting were recorded. Assessment of any pain experienced from the operative site was made by two methods and recorded at 1, 3, 6 and 18 hours postoperatively. Subjective assessment was made by the observer using a 10-cm linear analogue scale that read from no pain to severe pain. Objective assessment of the success of the local anaesthetic block was made by use of a simple measuring apparatus when the subjective assessment of pain indicated that little or no pain was experienced from the operative site.[3] The apparatus comprises an empty 50-ml intravenous infusion bag connected by a one-metre length of manometer tubing to an aneroid gauge that reads pressure in mmHg. The infusion bag contains 30 ml of air, sufficient to prevent the side walls from touching when the bag is compressed but insufficient to cause a positive reading at rest. With this device it was possible to apply a known pressure through thin surgical dressings to the wound site in order to test the effectiveness of the analgesia present. The ability to apply an arbitrary maximum pressure of 60 mmHg indicated a totally effective local anaesthetic block. The pressure bag measurements were recorded by one author (G.D.C.) at 3, 6 and 18 hours and by one of the two authors at 1 hour. The linear analogue assessment was made by G.D.C. at 3, 6 and 18 hours and at 1 hour by one of five recovery nurses who were trained to look after children in the recovery period.

Results

Patient and operative data. The two groups were comparable for age, weight and operative time, with no statistical difference between the two groups as shown by Student's *t*-test (Table 1).

Time taken for recovery from general anaes-

Table 1. Details of patients and operations.

	Age, years,	Weight, kg	Operative time, minutes	Operative data
Group A				
Range	1–12	9–45	30–80	11 Herniotomies
Mean (SD)	4.9 (2.6)	19.4 (7.9)	52 (13)	6 Orchidopexies
				2 Bilateral orchidopexies
				1 Herniotomy and orchidopexy
Group B				
Range	3–13	15–34	30–85	7 Herniotomies
Mean (SD)	5.8 (2.9)	21 (5.7)	49 (14.3)	11 Orchidopexies
				2 Bilateral orchidopexies
				1 Bilateral herniotomy

Table 2. Linear analogue pain scores.

	1 hour	3 hours	6 hours	18 hours
Group A				
Range, mm	0–20	0–45	0–20	0–30
Mean (SD), mm	2.5 (5.2)	5.7 (11.6)	5.7 (7.4)	12.2 (10.9)
Group B				
Range, mm	0–25	0–30	0–55	0–45
Mean (SD), mm	5.0 (7.9)	5.7 (10.8)	9.0 (15.2)	14.7 (11.4)

thesia. There was no significant difference between the two groups as to the time taken to recover from general anaesthesia as assessed by Student's *t*-test. Group A recovered in a mean of 34.7 minutes (SD 15.1) and group B in a mean of 29.8 minutes (SD 16.4).

Pain scores. The linear analogue pain scores and the results from the pressure bag were analysed by the Mann–Whitney *U* test and showed no significant difference between the two groups. The results from the linear analogue scales are shown in Table 2. The quality of the pain relief assessed from pressure applied through the bag, is shown in Fig. 1.

Additional analgesics. One patient of each group received paracetamol. Two patients from group B received intramuscular pethidine, one after 3 hours and the other after 11 hours.

Incidence and time of postoperative vomiting. There was no significant difference in the time of vomiting between the two groups (Student's *t*-test). Group A had a 70% incidence of vomiting after a mean of 277 minutes (SD 95) and group B an incidence of 66% after a mean of 394 minutes (range 110–1050, SD 261).

Time to first passing of urine. There was no significant difference in the time of first passing urine between the two groups as shown by Student's *t*-test. It was not possible to record the time of first micturition in the younger patients. Group A (n = 18) passed urine between 125 and 1005 minutes after surgery (mean 639 minutes) and group B (n = 19) between 140 and 1020 minutes (mean 631 minutes).

Time taken to complete the local anaesthetic technique. The caudal technique took between 3 and 10 minutes (mean 5.3 minutes) to complete whilst the nerve block and infiltration took 2–5 minutes (mean 3.1 minutes). This was significantly different ($p < 0.001$).

Complications. In the caudal technique difficulty in identification of the caudal canal was noted in one patient and blood was obtained on aspiration prior to injection of local anaesthetic on two occasions. In the nerve block and infiltration technique, a haematoma was noted in one patient.

Discussion

The results indicate that there is little difference in the quality of the postoperative analgesia provided by the two techniques. Both procedures have a similar duration of action and 50% of patients are pain free at rest 6 hours postoperatively. Therefore, any advantages gained from either the caudal or the nerve and field block approach must be assessed in relation to the convenience and technical ease of each method, the lack of complications and the reliability with which a successful block is produced.

The time of preparation prior to infiltration and nerve block is significantly less than for a caudal, when full asepsis including drapes, gloves and sterile tray is required. Both methods require a second anaesthetist to control the airway whilst the other performs the block and, by definition, both procedures are labour-intensive. The morbidity associated with the infiltration and nerve block technique is less than for caudal anaesthesia and the risks of major neurological complications, intrathecal injection or epidural vein puncture with possible intravenous injection, are eliminated. The only major risk of the nerve block technique is that of inadvertent bowel perforation.

Significantly, the total dose of local anaesthetic used for the nerve block and infiltration technique is less than that required for caudal anaesthesia. The former allows the total dose of bupivacaine to be limited to the recommended adult dose of bupivacaine of 2 mg/kg, even if bilateral blocks are required. The caudal technique, when the higher volume of 1.25 ml/kg is

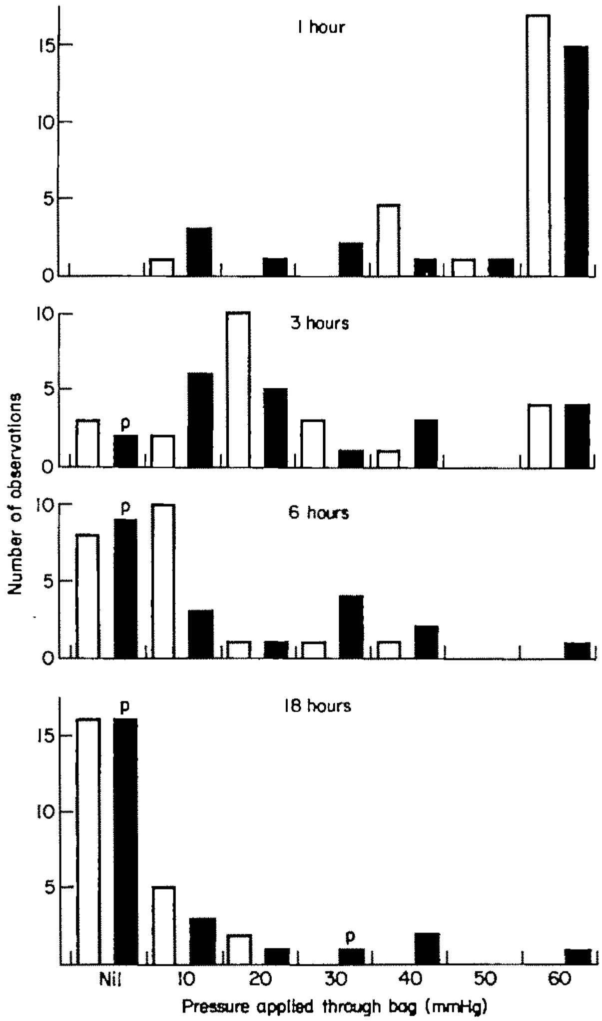

Fig. 1. Histograms showing the amount of pressure that was applied through the pressure bag to the wound sites before discomfort was experienced by each group of patients. The nil reading indicates the number of observations where discomfort was already experienced without the application of pressure to the wound site. The range of 10 mmHg to the arbitrary maximum of 60 mmHg indicates those observations in which the wound site would be free of pain when the patient was at rest. The P indicates the position of the two patients who received pethidine. □, Caudal group (group A); ■, iliohypogastric and ilio-inguinal nerve block group (group B).

used for orchidopexy, may reach a level of 3 mg/kg of bupivacaine, although this dosage has not been shown to produce toxic signs in young children.[4] For bilateral procedures, caudal anaesthesia has the advantage of providing analgesia for both sides from a single injection.

Technically, caudal anaesthesia has a definite end point with the penetration of the sacrococcygeal membrane followed by the free injection of local anaesthetic solution. Provided that a sufficient volume of local anaesthetic solution is injected, it produces good surgical analgesia. The demonstration of this surgical analgesia was seen during orchidopexy, when the manipulation

of the testis caused no change in the cardiac and respiratory rates, in contrast to the noncaudal group where the depth of general anaesthesia needed to be increased. However, the superior analgesia provided by caudal anaesthesia during surgery was not essential for adequate postoperative analgesia after orchidopexy, as demonstrated by the similarity of the postoperative pain scores in each group. This suggests that if caudal analgesia is used for postoperative pain relief after orchidopexy, the lower dosage of 1.0 ml/kg may be adequate in that it provides good lower abdominal and scrotal analgesia and may reduce the need to dilute the bupivacaine to 0.19% in as many patients.

There was no indication that the caudal group suffered bladder dysfunction or retention of urine when the time taken to pass urine postoperatively was compared between the two groups. In both groups there were patients who took up to 16 hours before first passage of urine. These prolonged times may reflect relative hypovolaemia as a result of the fluid restrictions placed on pre- and postoperative patients combined with increased fluid loss from vomiting. They may also have been observed because part of the postoperative survey was conducted at night, when urinary volumes are normally reduced.

The high incidence of postoperative vomiting in both groups is undesirable but is more common in children than adults and may reflect the use of opioid premedication or other factors such as anxiety or hypoglycaemia.

In both groups there were patients in whom the technique failed to provide more than 3 hours of satisfactory analgesia. The failures in the caudal group occurred possibly because there is no means of reliable control of the spread of anaesthetic solution once inside the caudal canal, which may lead to a reduced cephalad spread or unilateral block. The failures in the iliohypogastric and ilio-inguinal nerve block may have been due to the difficulty in identification of the external oblique aponeurosis. Identification of the latter may be helped by two methods: firstly, by use of a short, bevelled or slightly blunted needle to emphasise the resistance of the needle as it passes through the aponeurosis and, secondly, by advancing a sharp needle whilst it is moved from side to side in cephalad–caudad direction, at right-angles to the direction in which the fibres of the aponeurosis run, until the needle point has pierced these fibres when it should become fixed and prevent lateral movement.

The infiltration of local anaesthetic on the abdomen and, particularly, on the scrotum, requires surgical cooperation as to the proposed incisional site. The use of adrenaline in the bupivacaine not only emphasises the skin infiltration as shown by skin blanching, but local vasoconstriction reduces bleeding on incision and may reduce subsequent wound haematoma.

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Anaesthesia, 1987, Volume 42, pages 850–854

CASE REPORT

Basophil histamine release

A study in allergy to suxamethonium

D. E. WITHINGTON, K. B. P. LEUNG, L. BROMLEY, G. K. SCADDING AND F. L. PEARCE

Summary

A patient who suffered a severe hypotensive episode after induction of anaesthesia, was subsequently found to show positive skin-test responses to suxamethonium. Investigation revealed that suxamethonium induced basophils from the patient to release histamine to an extent comparable to that found after exposure to anti-IgE. Basophils from control subjects showed no such response. Basophil histamine release may offer a useful approach to the investigation of adverse drug reactions.

Key words

Complications; anaphylaxis.
Histamine; hypersensitivity, immediate.

Allergy to anaesthetic agents is a well-recognised problem.[1] Histamine has been implicated as a mediator in some adverse reactions during anaesthesia.[2] There are several mechanisms of histamine release, which include Type 1 (immediate) hypersensitivity, complement activation by the classical or alternative pathways, and direct action of a drug on basophils.[3] Current techniques of assessment in patients with suspected drug allergy, rarely allow a full understanding of the underlying mechanisms.

One approach which has been proposed in the investigation of such cases, is the measurement of histamine release by basophils exposed to potential allergens.[4] This technique allows a more direct assessment of the mechanism of the allergic response, but is seldom used. One previous report[5] suggested that basophils from patients sensitive to suxamethonium, release histamine when exposed to the drug in a reaction partly inhibited by acetylcholine. However, the authors did not address directly the role of IgE in the mediation of this effect, or the metabolic factors on which it depends.

This paper describes the use of basophil histamine release studies as part of the investigation of an adverse drug reaction which occurred during anaesthesia. We also investigated the role of IgE and other metabolic variables in the release of histamine from basophils in this patient.

Case history

A 35-year-old woman presented for a submucous resection as treatment for recurrent nasal conges-

D.E. Withington, MRCP, FFARCS, Senior Registrar, Department of Anaesthesia, St Thomas' Hospital, London SE1, K.B.P. Leung, PhD, Postdoctoral Research Assistant, Department of Chemistry, University College London, London WC1, L. Bromley, FFARCS, Senior Registrar, Department of Anaesthesia, The Middlesex Hospital, London W1, G.K. Scadding, MD, MRCP, Senior Registrar, Department of Clinical Immunology and Allergy, The Middlesex Hospital, London W1, F.L. Pearce, PhD, Reader, Department of Chemistry, University College London, London WC1.

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tion. She was non-atopic and had no significant past medical history. She had previously been anaesthetised uneventfully for tonsillectomy and surgery to her jaw. She was receiving no medication. On pre-operative assessment she was a fit young woman who presented no obvious anaesthetic hazards.

Induction of anaesthesia was with thiopentone 400 mg followed by suxamethonium 100 mg, and tracheal intubation was performed. Spontaneous respiration returned and nitrous oxide 66% in oxygen with halothane was administered. During the nasal installation of Moffett's solution, cyanosis occurred and both peripheral and carotid pulses became impalpable. External cardiac massage was started and the lungs were ventilated with 100% oxygen. Hydrocortisone 100 mg, plasma protein fraction 1 litre and Hartmann's solution 1 litre were given, with rapid return of carotid pulses. An electrocardiogram showed no evidence of cardiac dysrhythmia. Bronchospasm was not a feature of this reaction at any stage. The operation was abandoned and consciousness returned after 40 minutes but, due to the patient's extreme agitation, it was decided to sedate and ventilate her overnight. The following morning, spontaneous respiration was resumed, her trachea was extubated without incident and she remained well. At the time of the collapse some facial oedema was noted which had subsided by morning.

Investigation

Blood samples were taken for a full blood count, measurement of serum complement (C_3 and C_4) concentration and IgE levels (Table 1). Skin tests were performed according to the protocol of Fisher.[6] The agents tested were thiopentone, methohexitone, suxamethonium and all commonly used non-depolarising neuromuscular relaxants apart from vecuronium. Basophil histamine release in response to suxamethonium was then studied in samples from the patient and from a control group of 10 normal individuals.

Method

Blood samples were obtained from 10 normal non-atopic controls and from the patient. Twenty millilitres of blood were collected into preservative-free heparin. Dextran 110 in normal saline was added (1 ml to 4 ml blood), together with glucose 6 mg/ml blood. The erythrocytes were then allowed to sediment for 45 minutes at room temperature and the leucocyte-rich plasma recovered. The cells were separated from plasma by centrifugation, washed in Tyrode's solution and resuspended. All experiments were performed in Tyrode's solution at pH 7.4. The cells were incubated with dilutions of rabbit anti-human IgE, dilutions of suxamethonium, or dilutions of suxamethonium in the presence of anti-IgE at a concentration of 1:3000. Incubation was for 25 minutes at 37°C. The reaction was stopped with ice-cold buffer, the samples centrifuged and the supernatant decanted. Buffer was added to the cells to equal volumes and perchloric acid added to all samples to lyse cells. The histamine contents were assayed using a Technicon Autoanalyser Mark 2.

Further studies investigated the mechanism of suxamethonium-induced histamine release. Among the factors studied were the effects of calcium and magnesium, and the action of the metabolic inhibitors antimycin A and 2-deoxyglucose. Results were corrected for the spontaneous release from unchallenged cells and expressed as a percentage of total cellular histamine.

Results

General investigations

Pre-operative and 24 hour post-incident white cell counts were normal. Differential count was

Table 1. Clinical details.

	Pre-operative	24 hours after incident
Haemoglobin (g/dl)	13.4	12.5
White cell count	7.7	5.1
Complement (g/litre)		
C_3	—	0.49 (normal 0.75–1.6 g/litre)
C_4	—	0.3 (normal 0.20–0.65 g/litre)
IgE (U/ml)	—	4000.0 (normal 5–120 U/ml)

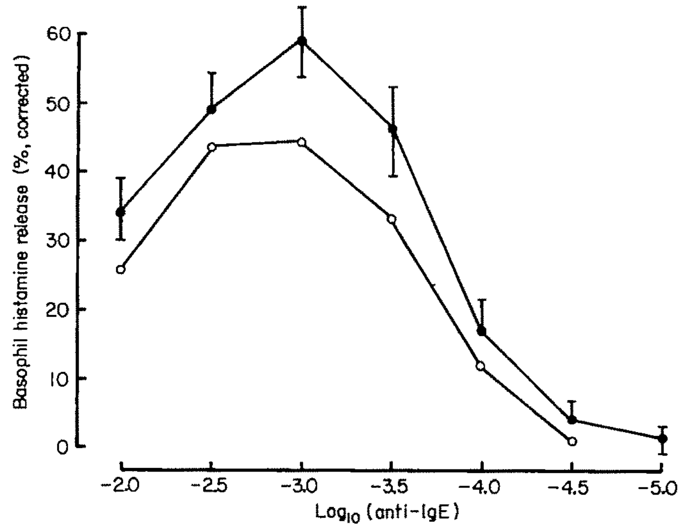

Fig. 1. Basophil histamine release from control and patient basophils in response to rabbit anti-IgE. ●, Control basophils, mean (SEM); ○, patient basophils.

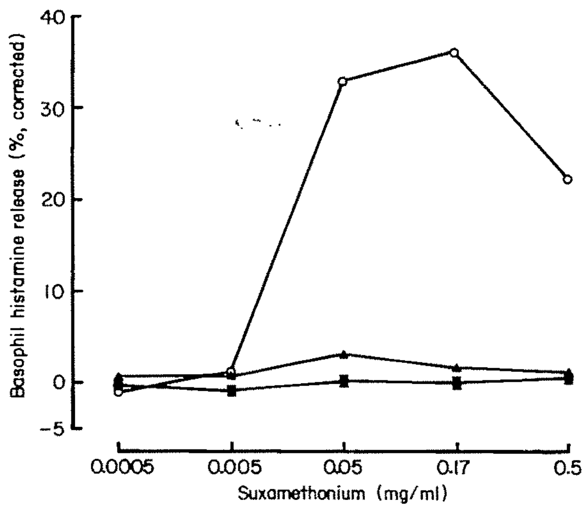

Fig. 2. Basophil histamine release from control and patient basophils in response to suxamethonium. ●, Control basophils, mean (SEM); ○, patient basophils, in full Tyrode's solution; ▲, patient basophils, in calcium/magnesium-free buffer.

not available. The C_3 component of the serum complement was decreased, which implies complement activation via the alternative pathway. The IgE level was noted to be elevated (Table 1).

Skin tests

Prick tests were negative for all the agents tested and a control histamine injection produced a normal weal. Intradermal testing showed a strong positive reaction to suxamethonium alone (drug concentration 1:10 000).

Basophil histamine release studies

Cells from 10 normal controls and from the patient showed normal dose–response curves to anti-IgE (Fig. 1). No histamine was released by basophils from control subjects when incubated

Table 2. Basophil histamine release by cells from 10 control subjects and from a patient with proven allergy to suxamethonium.

Suxamethonium (mg/ml)	Control cells Anti-IgE 1:3000 Mean (SEM)	Patient cells Anti-IgE 1:3000	Patient cells 2-Deoxyglucose + antimycin A
0.5	42.2 (5.8)	34.2	1.4
0.17	45.8 (5.5)	36.9	0.8
0.05	50.1 (5.4)	38.6	1.0
0.005	46.6 (5.2)	33.4	−0.1
0.0005	42.7 (5.4)	36.2	−0.2
Spontaneous release	<6.7%	<3.8%	

in the presence of suxamethonium in dilutions of from 0.5 to 0.0005 mg/ml. However, cells from the patient released histamine in a dose-dependent manner in response to these suxamethonium concentrations (Fig. 2). When incubated with suxamethonium dilutions in the presence of anti-IgE, cells from controls and from the patient released the same amount of histamine as when exposed to the same concentration of anti-IgE alone (Table 2).

Suxamethonium-induced histamine release by the patient's cells was found to be calcium/magnesium dependent; it was abolished when calcium/magnesium-free Tyrode's solution was substituted (Fig. 2). Histamine release was also abolished by the presence of the metabolic inhibitors 2-deoxyglucose and antimycin A (Table 2).

Discussion

The incidence of adverse drug reactions during anaesthesia is generally accepted as being one per 5–20 000 general anaesthetics. Reactions to muscle relaxants are probably more common than those to induction agents and are often caused by IgE-mediated mechanisms.[7] Investigation of such reactions usually comprises the use of skin tests and little is known of the cellular responses of susceptible individuals to specific antigens.

The use of direct measurement of histamine release from basophils was recommended by Laxenaire and co-workers[4] and has been utilised by Vervloet *et al.*[5,8] in the investigation of similar cases. However, the technique remains little used in the investigation of drug reactions. The present report studied the response to exposure to suxamethonium, of circulating basophils from a woman who had suffered a severe adverse reaction and in whom skin testing had indicated that suxamethonium was the cause. Hypotension and oedema, the two main adverse effects noted in the patient, have been noted previously to be frequent elements in reactions to muscle relaxants.[7] Basophils from 10 control subjects demonstrated a reproducible dose-dependent histamine release following challenge with anti-IgE. Suxamethonium failed to release histamine from these normal basophils and the presence of the drug did not alter histamine release in response to anti-IgE.

The patient's cells responded to anti-IgE in a manner comparable to those from the control subjects. However, suxamethonium caused a dose-dependent release of histamine; the maximum effect was seen at a drug concentration of 0.05 mg/ml. This release was demonstrated to be calcium/magnesium dependent and to occur by a metabolically active process. No additional histamine release by suxamethonium was noted in the presence of anti-IgE. One possible explanation is that suxamethonium caused a reaction at a cell-surface site shared with anti-IgE. This interpretation appears likely because of the patient's positive skin-testing responses to suxamethonium and her elevated IgE levels. Our study design, which was limited by the availability of the patient's blood, did not allow us to investigate the alternative interpretation, that the basophils were fully stimulated by anti-IgE and that the cells were capable of no further release by suxamethonium.

This preliminary report suggests that estimation of histamine release by basophils exposed to suspected antigens *in vitro*, may prove an effective, noninvasive method for the investigation of drug reactions which are thought to have

an immunological mechanism. Further studies are required to define the cellular sites responsible for the mediation of histamine release in subjects who react positively to the test.

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CASE REPORT

Hypercholinesterasaemia and suxamethonium resistance

P. WARRAN, M. THEEMAN, A. M. BOLD AND S. JONES

Summary

A case is reported of resistance to the muscle relaxing action of suxamethonium due to the rare inherited condition of hypercholinesterasaemia. Family studies suggest dominant inheritance. It is suggested the condition should be considered whenever there is unexpected resistance to the muscle relaxing action of suxamethonium.

Key words

Enzymes; plasma cholinesterase.
Neuromuscular relaxants; suxamethonium.

Sensitivity to the action of suxamethonium that leads to prolonged apnoea is associated with abnormalities of the enzyme cholinesterase and has been reviewed recently.[1] The opposite condition, in which there is resistance to the muscle relaxing action of suxamethonium, is due to hypercholinesterasaemia. It is much less recognised.[2,3] We report a case of hypercholinesterasaemia and a study of the family.

Case history

A 32-year-old Saudi female, weight 45 kg, was scheduled for bilateral antral wash-outs, excision of a nasal cyst and submucous diathermy. She was clinically well. It was noted that she had a dental bridge capping to three front teeth. Anaesthesia for dilatation and curettage 2 years previously had apparently been uneventful.

She was premedicated with diazepam 10 mg orally 2 hours pre-operatively. Anaesthesia was induced with thiopentone 250 mg and fentanyl 50 μg, followed by suxamethonium 60 mg administered intravenously via a butterfly cannula. The vocal cords were still active at intubation. This failure of the cords to relax was attributed, at the time, to possibly improper storage of the suxamethonium ampoule. The patient was allowed to breathe spontaneously a mixture of nitrous oxide, oxygen and halothane. The operation proceeded uneventfully.

One month later, the patient was re-admitted to hospital for removal of the cyst which had been found to be of dental origin. She was premedicated with intramuscular morphine 10 mg and atropine 0.3 mg one hour prior to surgery. Anaesthesia was induced with thiopentone 300 mg, followed by suxamethonium 100 mg. Again, at intubation the vocal cords were found to be active. The batch of ampoules from which the

P. Warran, MB, ChB, FFARCS, Senior Registrar, M. Theeman, MB, BS, FFARCS, Senior Consultant, A.M. Bold, BM, BCh, FRCPath, Consultant Chemical Pathologist, King Khalid Hospital, Jeddah, S. Jones, PhD, Senior Biochemist, Clinical Chemistry Department, Queen Elizabeth Hospital Medical Centre, Birmingham.

Correspondence should be addressed to Dr A.M. Bold, Pathology Department, National Guard King Khalid Hospital, P.O. Box 9515, Jeddah, Kingdom of Saudi Arabia.

suxamethonium had been taken was known to be satisfactory, so blood was taken for determination of serum cholinesterase. The result was significantly elevated, at 55 U/litre (reference range 7–19 U/litre, Dupont ACA method). The high serum cholinesterase was confirmed by a repeat determination 2 days later, when the serum cholinesterase was 52 U/litre. The relevance of the manufacturer's reported reference range was checked by measurements of serum cholinesterase in 15 Saudi control patients, in all of whom the serum cholinesterase was below 19 U/litre. Plasma glucose, total and free thyroxine, serum albumin and globulin, bilirubin, alkaline phosphatase and aspartate aminotransferase were all within normal limits.

The patient, her husband and children had serum cholinesterase determinations. The results are shown in Table 1.

Separation of the cholinesterase enzymes in the patient's serum by polyacrylamide electrophoresis[4] showed marked differences when compared with similarly treated normal serum (Fig. 1). In normal sera, there is a strong band of cholinesterase activity (band 2 in Fig. 1) and a number of fainter bands. All these bands were slightly increased in the patient's serum, but the most striking feature was the presence of a strong band of activity (band 1, samples 2 and 5 in Fig. 1). This band is not detectable in normal serum, and moves more slowly than the predominant normal band 1 in samples 1, 3, 4 and 6 (Fig. 1). Inhibition with lysivane and studies using acetyl beta-methyl thiocholine and butyryl thiocholine as substrates, showed that bands 1 and 2 had similar characteristics. Comparison with fetal serum samples after prolonged electrophoresis, demonstrated that the cholinesterase form of band 1 differed from that of fetal origin described previously.[4]

Table 1. Serum cholinesterase results in family of the patient.

	Age	Sex	Serum cholinesterase (U/litre)
Patient	32	F	63
Husband	58	M	19
Child 1	17	M	40
Child 2	14	M	47
Child 3	13	F	14
Child 4	10	M	40
Child 5	8	M	15
Child 6	5	M	19
Child 7	3	M	55

Discussion

The patient was found on three occasions to have serum cholinesterase activity about three times the upper limit of normal. This was confirmed by Dr M. Whittaker at the Cholinesterase

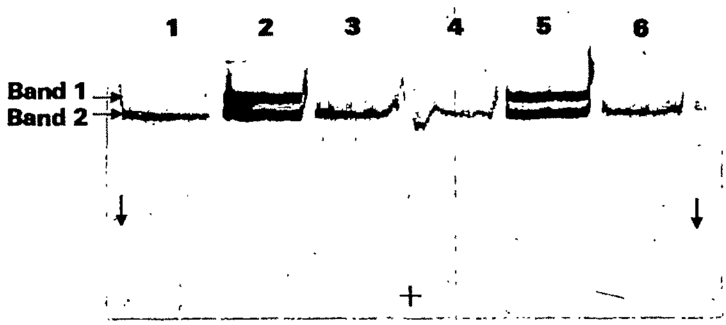

Fig. 1. Bands of cholinesterase activity in the patient's serum (samples 2 and 5) compared with serum of normal activity (samples 1, 3, 4 and 6). The enzyme was incubated with acetylthiocholine in the presence of copper sulphate and the copper thiocholine precipitate produced was visualised using dithiooxamide. Band 2 is the most intense activity band seen in the samples of normal activity; the minor activity bands are not shown here.

Research Unit in Exeter, where the fluoride and dibucaine numbers were found to be normal (62 and 83, respectively; genotypically E_1^u, E_1^u). Known causes of elevated serum cholinesterase activity such as obesity, diabetes mellitus, hepatitis (recovery phase), hyperthyroidism and the nephrotic syndrome were excluded in this patient. The results of the family study demonstrate that this was a case of congenital hypercholinesterasaemia. The results are compatible with dominant inheritance, as has been shown in previously reported cases,[2,3] although we have been unable to conduct more extensive family studies to establish this absolutely. The acrylamide gel studies suggest the inheritance of an additional isoenzyme. The clinical observation of resistance to the muscle relaxing action of intravenous suxamethonium indicates that this isoenzyme has full biological activity. The paucity of reported cases of hypercholinesterasaemia suggests that this is a rare condition but it is possible that it is under-diagnosed. We suggest that it should be excluded by determination of serum cholinesterase in all patients who appear to be resistant to the action of normal doses of suxamethonium.[5]

Acknowledgment

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CASE REPORT

Prolongation of neuromuscular blocking effect of vecuronium by antibiotics

R. JEDEIKIN, E. DOLGUNSKI, R. KAPLAN AND S. HOFFMAN

Summary

A case is described of prolonged neuromuscular block in a patient who was given the muscle relaxant vecuronium followed by bolus injections of the antibiotics gentamycin and clindamycin.

Key words

Antibiotics; gentamycin, clindamycin.
Complications; prolonged neuromuscular blockade.

Vecuronium is an intermediate acting, non-depolarising muscle relaxant. Time for full recovery of muscle action following a single dose of vecuronium (which produces 90% depression of muscle contraction) is approximately one-third of that after an equipotent dose of pancuronium.[1,2] However, the duration of neuromuscular block following an exaggerated high dose of 0.2 mg/kg is not more than 120 minutes.[3] We report a case of prolonged neuromuscular block thought to be due to interaction between vecuronium and the antibiotics gentamycin and clindamycin.

Case history

A 52-year-old female with a history of hypertension and congestive heart failure controlled with digoxin 0.25 mg/day, nifedipine 20 mg/day and frusemide 40 mg biweekly, presented for elective removal of a carcinoma of the colon. Her general condition before surgery was stable, she was not in heart failure and her arterial blood pressure was 170/90 mmHg. Liver function was normal, as were her serum electrolytes and acid–base status. Premedication was with oral diazepam 10 mg, 2 hours before surgery, and pethidine 50 mg and promethazine 25 mg intramuscularly one hour before surgery. Anaesthesia was induced with intravenous midazolam 9 mg, fentanyl 0.05 mg and lignocaine 100 mg and the trachea intubated after 75 mg suxamethonium. After recovery from the suxamethonium, vecuronium 0.08 mg/kg (4 mg) was injected intravenously. Monitoring of neuromuscular block was by continuous recording of the train-of-four (TOF) using ulnar nerve stimulation. Ten minutes after the vecuronium was given, gentamycin 120 mg and clindamycin 1200 mg were given as a bolus. Maintenance of anaesthesia was with 50% nitrous oxide in oxygen and fentanyl 0.3 mg in divided doses. Marked neuromuscular blockade was still present 160 minutes after the initial injection of vecuronium

R. Jedeikin, FFA (SA), Lecturer, E. Dolgunski, MD, Tutor, R. Kaplan, MD, Lecturer, S. Hoffman, MMed (SA), Professor, Department of Anaesthesia, Meir Hospital, Kfar Saba, Sackler School of Medicine, University of Tel Aviv, Israel.
* Correspondence should be addressed to R. Jedeikin, Director, ICU, Meir Hospital, Kfar Saba, Israel.

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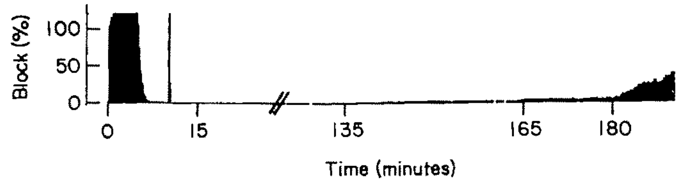

Fig. 1. Prolonged neuromuscular block during continuous recording of train-of-four ulnar nerve stimulation.

and was confirmed by a minimal twitch response, which was 2% of the control (Fig. 1). (Twitch response is the height of the first twitch in the train of four compared with the control.) Thereafter muscle twitch recovery was fairly rapid; 30% recovery was observed at 180 minutes and 50% recovery at 190 minutes. Surgery was completed at the latter time and the patient was able to breathe spontaneously.

Neostigmine 2.5 mg and atropine 1.0 mg were administered intravenously and extubation performed. Postoperative recovery was uneventful.

Discussion

Vecuronium is a potent, medium acting, non-depolarising muscle relaxant. Like other neuromuscular blocking agents it blocks the prejunctional receptors, reduces the mean quantal content of the endplate potential and also blocks the postjunctional receptors prior to occlusion of any ion channels.[4] The relatively short duration of neuromuscular block with vecuronium is well established.[1,2,5,6] It is said to be about a third of that given by pancuronium, and 0.1 mg/kg vecuronium has been shown to cause neuromuscular block for 36 minutes (SEM 2.1) from the start of the injection until its return to 25% of control twitch height.[5] In our patient, 0.08 mg/kg vecuronium resulted in 3 hours of neuromuscular block, after which time 30% recovery was observed.

This prolonged block is more than five times the duration observed by Duncalf *et al.*[6] who used a similar dose of vecuronium (0.1 mg/kg) in patients who received neuroleptanaesthesia.

Muscle blockade by non-depolarising muscle relaxants may be augmented by volatile anaesthetic agents, by electrolyte imbalance including low serum potassium, low calcium and increased magnesium, calcium antagonists, by diuretics and by the concurrent use of antibiotics. Prolongation of the action of vecuronium may also be predicted in patients with liver disease, since it is eliminated predominantly by hepatic excretion.

The serum electrolytes and liver function in our patient were normal and no volatile anaesthetics had been administered. It has recently been shown that the calcium antagonist verapamil can enhance the actions of neuromuscular blocking agents.[7–9] Prolonged neuromuscular block was shown to occur in laboratory animals that received verapamil in doses several times greater than the usual dose in clinical use.[9] To the best of our knowledge there has been one clinical report of a patient in renal failure who was receiving intravenous verapamil, where prolonged neuromuscular block occurred on addition of vecuronium.[10] We cannot rule out a synergistic effect of nifedipine and vecuronium in our patient but we believe it highly unlikely since she received only 20 mg nifedipine a day; the last dose was administered the evening before surgery. It therefore appears likely that the administration of parenteral antibiotics 10 minutes after the injection of vecuronium caused the prolonged neuromuscular blocking effect of the vecuronium. That antibiotics can produce neuromuscular block alone or potentiate the neuromuscular blocking effect of non-depolarising muscle relaxants is well established, as are the neuromuscular blocking effects of gentamycin and clindamycin in association with other non-depolarising muscle relaxants.[11] However, we were unable to find any reports of the prolongation of vecuronium neuromuscular block by gentamycin, clindamycin or any other antibiotics. Krieg and his associates[12] did show a potentiation of neuromuscular block by gentamycin and clindamycin in rats and cats that received vecuronium, but were unable to demonstrate a prolongation

of neuromuscular block. Both gentamycin and clindamycin are thought to act on the presynaptic as well as postsynaptic sites of the neuromuscular junction. However, the action of clindamycin on neuromuscular function is complex. Clindamycin has been shown to have a local anaesthetic effect on the nerve, as well as a blocking action of pre- and postsynaptic cholinergic receptors.[11,13] Its main neuromuscular blocking affect appears to be by a direct depressant action of the muscle.[11]

Of all the antibiotics, gentamycin is that most often associated with the potentiation of neuromuscular block by non-depolarising muscle relaxants. Current data suggest that the predominant neuromuscular blocking action of gentamycin is on the presynaptic site of the neuromuscular junction and that it exerts a magnesium-like effect in the reduction of quantum transmitter release, while the postjunctional action of gentamycin is thought to be of little importance.[11]

The combination of an aminoglycoside and clindamycin for prophylaxis during abdominal surgery is commonly used in our hospital and appears to be safe and effective. However, peak blood levels will tend to occur when bolus injections of large doses of antibiotics such as gentamycin and clindamycin are administered intravenously. We may find that if more frequent use is made of neuromuscular monitors, an increase in the number of cases of prolonged neuromuscular block will be observed and that the true incidence of antibiotic potentiation of neuromuscular block will be established. Postoperative respiratory depression is a condition that is frequently diagnosed in the recovery room and usually managed adequately by a short period of artificial ventilation until the return of normal respiratory function. It is, more often than not, attributed to overzealous use of anaesthetic agents especially in the elderly patient. We may well find that antibiotic therapy given during anaesthesia is a major factor that contributes to postoperative respiratory depression.

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CASE REPORT

Histamine levels and cardiovascular responses during splenectomy and splenorenal shunt formation in a patient with systemic mastocytosis

G. B. SMITH, R. J. GUSBERG, R. H. JORDAN AND B. KIM

Summary

Systemic mastocytosis is a rare disorder characterised by the infiltration of many tissues by abnormal numbers of mast cells. Life-threatening episodes of bronchospasm and hypotension are common in response to a variety of triggers which cause mast cell degranulation. We present the case history of a patient with severe mast cell disease who successfully underwent splenectomy and portocaval anastomosis. Peri-operative therapy was directed towards mast cell stabilisation, and histamine-releasing drugs were avoided. Cardiovascular data, together with blood histamine levels and thrombin times, indicated that mast cell degranulation did not occur. A review of the current literature concerning mast cell disease as it relates to anaesthesia is presented and suggestions for the safe management of such cases are given.

Key words

Co-existing disease; systemic mastocytosis.
Complications; histamine release.

Systemic mastocytosis is an uncommon disorder characterised by proliferation of mast cells which may infiltrate many organs of the body.[1] Mast cells release several biologically active substances in response to many triggers, including stress, trauma, extremes of temperature, biological polymers and drugs. Minor symptoms of mast cell degranulation include weakness, fatigue, diarrhoea, pruritus, abdominal pain and flushing of the skin. Tachycardia, hypotension, syncope and death may also occur. Symptoms and signs of degranulation have generally been attributed to the release of histamine, but recent studies[2,3] have implicated the prostaglandin PGD_2. Histamine relaxes smooth muscle of arterioles, which leads to a decrease in systemic vascular resistance and arterial blood pressure. It causes capillary vasodilatation and increases both capillary permeability and myocardial contractility. Smooth muscle of the gut and bronchi contract, and acid and pepsin secretion from the stomach is increased. Mast cells also contain heparin, and coagulopathy may result from its release.

The anaesthetic management of patients with mast cell disease has been outlined recently[4,5] but there are few case histories of surgery and anaesthesia in the literature.[5–8] Demis[9] demonstrated a four-fold increase in urinary histamine excretion following operation; however, there

G.B. Smith, BM, FFARCS, Instructor in Anesthesiology, R.J. Gusberg, MD, Associate Professor in Surgery, R.H. Jordan, MD, Resident in Anesthesiology, B. Kim, MD, Instructor in Surgery, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA.

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are no published reports of haemodynamic parameters, coagulation studies and blood histamine levels during anaesthesia and surgery.

We report the case history of a patient who suffered from systemic mastocytosis and underwent anaesthesia for splenectomy and the formation of a portocaval shunt. Blood histamine levels and thrombin times are presented in addition to cardiovascular data.

Case history

A 39-year-old male with systemic mastocytosis was admitted for elective splenectomy and a splenorenal shunt procedure. Diagnosis of systemic mast cell disease had been confirmed 8 years earlier when a routine physical examination had revealed massive splenomegaly. Since then, the patient's main symptoms had been recurrent pruritus and diarrhoea. Between 1978 and 1984, he suffered four major episodes of upper gastrointestinal haemorrhage which required hospitalisation and transfusion. In 1978 and 1980, these were complicated by acute renal failure; the second episode required temporary haemodialysis. A transient coagulopathy, thought to be related to heparin release from mast cells, was noted during the episode in 1978. An earlier upper gastrointestinal endoscopy did not reveal any abnormality but a subsequent examination in 1983 demonstrated large oesophageal varices. Medical treatment to this date had comprised oral cimetidine and oral sodium cromoglycate. Injection sclerotherapy of his oesophageal varices was undertaken on three occasions in 1983 and 1984.

Seven months prior to admission, portal hypertension was demonstrated at abdominal angiography and a liver biopsy showed cirrhosis with infiltration of the liver by nests of mast cells. Both angiography and liver biopsy were complicated by abdominal cramps which were relieved by administration of diphenhydramine and cimetidine. Haematological evaluation revealed a prolonged bleeding time with a low factor VIII level (34%), which suggested von Willebrand's disease. Normal factor VIII levels were demonstrated in both of the patient's parents. However, a bone marrow aspiration performed several days prior to surgery was associated with marked haemorrhage for one and a half hours.

On admission, the patient was noted to be thin, pale and wasted with a protuberant abdomen. There was no evidence of urticaria pigmentosa but examination of the skin did reveal several spider naevi over the head and upper thorax. Pre-operative pulse rate was 92 beats/minute and arterial blood pressure 110/60 mmHg. Heart sounds were normal but a pansystolic murmur was heard at the left sternal edge and apex (on the basis of echocardiographic evaluation, the murmur was thought to be benign). Lung fields were clear. The liver was enlarged to approximately 14 cm in span and extended 3–4 cm below the right costal margin. A hard, nodular spleen was palpable below the umbilicus. Rectal examination revealed haemorrhoids.

Pre-operative laboratory investigations were normal except for moderate anaemia (Hb 9.2 g/dl), increased alkaline phosphatase (137 U/litre, normal 10–70 U/litre) and a decreased factor VIII level of 45% (normal 60–200%).

Oral therapy with sodium cromoglycate and cimetidine was continued until the evening prior to surgery. One and a half hours before the induction of anaesthesia, the patient received oral diazepam 10 mg with hydrocortisone 100 mg, cimetidine 300 mg and diphenhydramine 50 mg administered intravenously The dose of diphenhydramine was repeated on arrival in the operating room, and the patient further sedated with increments of fentanyl and diazepam to allow insertion of a radial artery cannula, large bore intravenous cannulae and a thermodilution cardiac output pulmonary artery catheter. The electrocardiogram was monitored continuously using the CM5 configuration. A warming blanket was used to maintain temperature.

Anaesthesia was induced with a mixture of isoflurane and oxygen in 50% nitrous oxide. Muscle relaxation to facilitate tracheal intubation was achieved with pancuronium 8 mg following loss of consciousness. A urinary catheter, oesophageal stethoscope, oesophageal temperature probe and nasogastric tube were then inserted.

Anaesthesia was maintained initially with isoflurane 1.5% in 70% nitrous oxide and oxygen but, because of an unexplained tachycardia, the isoflurane was discontinued and enflurane 1% substituted. The tachycardia gradually abated during the course of surgery. Ventilation was adjusted to obtain normocarbia. Supplemental doses of pancuronium and fen-

tanyl, and repeat boluses of diphenhydramine 50 mg and cimetidine 300 mg were administered 6 hours after the initial dose. Mannitol 10%, 250 ml, was given to treat oliguria in the presence of adequate left ventricular filling pressures.

Blood samples were drawn throughout the surgical procedure to allow monitoring of thrombin times and to assess blood gas tensions. Further specimens of blood without coagulant were immediately frozen in combination with potassium oxalate for subsequent analysis of whole blood histamine levels using the method described by Huff *et al.*[10] Cardiovascular data were obtained from the monitoring catheters described previously.

Figure 1 shows the pertinent intra-operative cardiovascular data obtained during anaesthesia and their relationship to whole blood histamine levels. Cardiac output (CO) was computed using an Edwards thermodilution cardiac output computer (Model 9520); total systemic resistance (TSR) was then calculated as TSR = BP/CO.

There were no episodes of flushing, bronchospasm or hypotension during the operation, and clinically significant alterations in haemodynamic parameters were not seen. Whole blood histamine levels remained within the normal range (3–9 μg/100 ml) at all times. Figure 1 demonstrates that total systemic resistance remained in the normal range until after splenectomy; however, no relationship exists between either histamine levels and total systemic resistance or histamine levels and cardiac output.

Thrombin times were elevated before anaesthesia but no further clinically significant in-

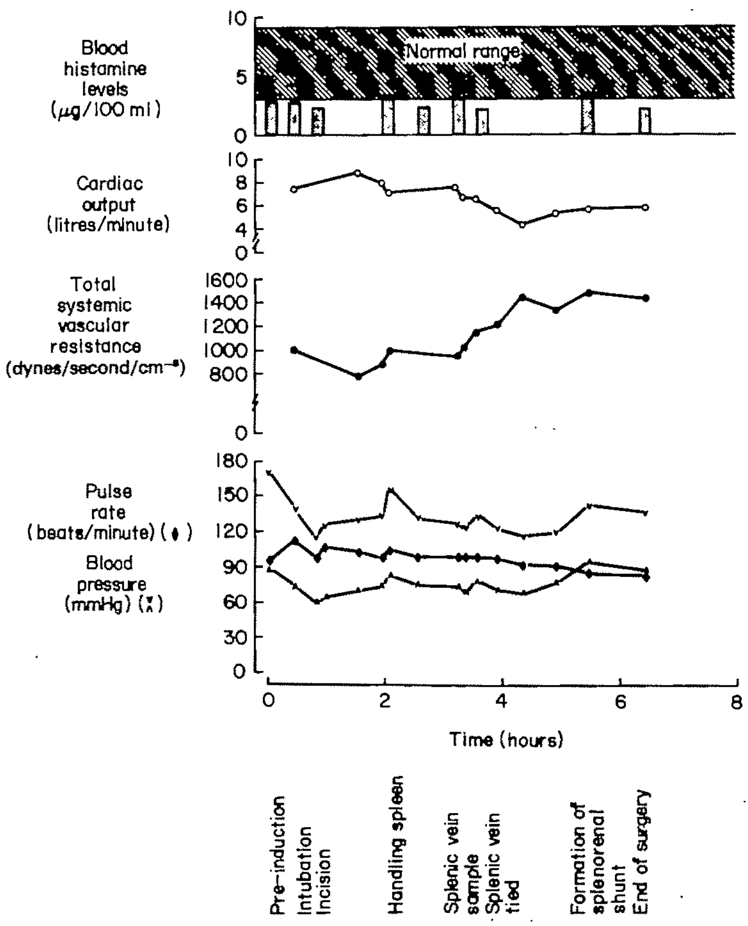

Fig. 1. Blood histamine levels and cardiovascular measurements during anaesthesia in a patient with systemic mastocytosis.

crease in these values occurred during surgery. All remained slightly elevated (normal 20–25 seconds: < 5 seconds above control) but did not require treatment. There was no relationship between thrombin time and histamine levels. The duration of anaesthesia and surgery was 8 hours. The patient underwent splenectomy and central splenorenal shunting. Reversal of residual paralysis was accomplished using neostigmine 2.5 mg and glycopyrronium 0.6 mg. The patient was transported to the surgical intensive care unit in a stable condition following tracheal extubation. Total blood loss during operation was approximately 1500 ml, and urine output was 565 ml. Fluid replacement consisted of 3 units whole blood, 1 unit packed red cells, 5950 ml lactated Ringer's solution and 250 ml mannitol 10%.

Intravenous diphenhydramine and cimetidine were continued in the postoperative period, together with doses of hydrocortisone which were gradually reduced and discontinued on the third postoperative day. Therapy with sodium cromoglycate was restarted immediately after operation on a 6-hourly basis, administered initially via the nasogastric tube and later by mouth. Postoperative pain relief was achieved initially with intravenous fentanyl and later with intramuscular nalbuphine. A satisfactory postoperative recovery, complicated only by moderate ascites, was obtained and the patient was discharged on the eighth postoperative day.

Discussion

Systemic mastocytosis is of importance to the anaesthetist for two major reasons. First, infiltration of many of the body organs, including liver, spleen, bones, lymph nodes and skin, may result in anaemia, thrombocytopenia, osteoporosis, pathological fractures, hepatosplenomegaly and a bleeding diathesis. Second, mast cell degranulation results in the release of many vasoactive and other substances which may cause hypotension, tachycardia, bronchospasm and coagulopathy. Previously, the majority of these effects were attributed to histamine release but recently, a prostaglandin, PGD_2, has been implicated.[2,3,11] Other chemical mediators activated or released by mast cell degranulation include eosinophilic chemotactic factor of anaphylaxis, leukotrienes, 5-hydroxytryptamine and platelet activating factor.[12]

Degranulation of the mast cells can occur through either immunological (antigen–IgE combination) or nonimmunological (drugs, cold and stress) mechanisms and is a direct result of a decrease in intracellular cyclic adenosine monophosphate (cAMP). Agents capable of increasing cellular cAMP have been used to modify and prevent mast cell degranulation (Fig. 2). These include prostaglandins of the E series. beta-adrenergic drugs (e.g. isoprenaline, adrenaline) and the phosphodiesterase inhibitors (i.e. methylxanthines).[12,13]

The chronic treatment of systemic mast cell disease has classically involved the use of drugs which block the peripheral actions of histamine (H_1 or H_2 receptor antagonists), or the mast cell stabiliser, sodium cromoglycate. H_1 receptors exist on all smooth muscle cells and are responsible for the vascular and respiratory effects of histamine. H_2 receptors exist on gastric parietal cells (acid and pepsin secretion), mast cells (where they act as a feedback to prevent further degranulation[14]) and on vascular smooth muscle. Hypotension due to capillary dilatation is thought to be mediated by both types of histamine receptors.[15]

Sodium cromoglycate has no direct antihistamine activity and can only be used prophylactically. It may act by prevention of calcium influx at the cell membrane, thereby preventing activation of degranulation.[12] Oral sodium cromoglycate given every 6 hours has produced a dramatic improvement in cutaneous, gastrointestinal and central nervous system symptoms.[16] H_1 and H_2 receptor antagonists have been used alone or in combination in the treatment of systemic mastocytosis. In general, H_2 receptor antagonists, such as cimetidine, are useful in the management of patients with gastrointestinal symptoms,[17] but combined H_1 and H_2 receptor antagonist therapy appears to be more effective when a more extensive disease process is present.[18] Despite these reports, the effect of H_1 and H_2 receptor antagonists has been disappointing during episodes of hypotension and severe flushing.[2,3] The drug of choice in this situation is adrenaline administered preferably by the intravenous route or, alternatively, subcutaneously.[3,6]

The demonstration of increased production of prostaglandin PGD_2 in patients with systemic mastocytosis[2,3,6] and the improvement in symptoms that follows the use of prostaglandin syn-

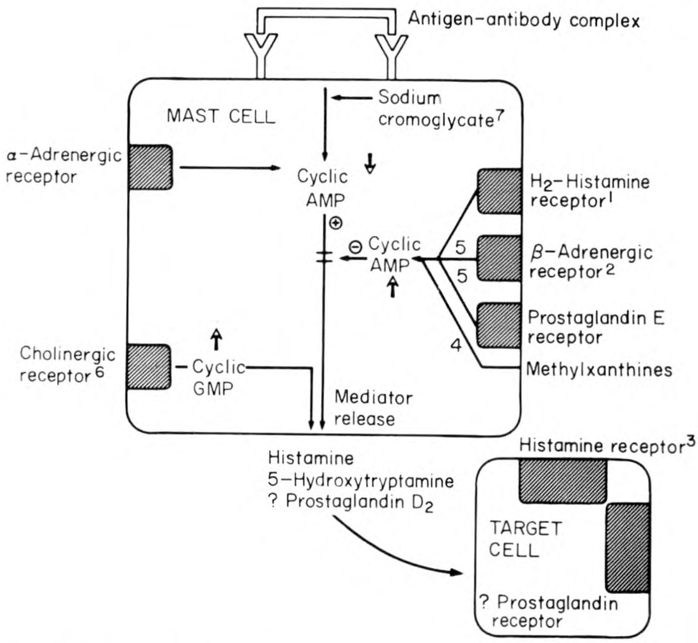

Fig. 2. Factors that affect mediator release from mast cells and prevention of target organ effect. 1, Blocked by cimetidine; 2, blocked by propranolol; 3, blocked by antihistamines; 4, phosphodiesterase inhibition; 5, stimulation of adenyl cyclase; 6, blocked by atropine; 7, prevents calcium influx.

thetase inhibitors, such as acetyl salicylic acid (aspirin), in patients in whom antihistamine therapy has failed, has recently altered the understanding of mast cell disease. Studies in dogs have demonstrated that PGD_2 can account for most of the signs and symptoms of systemic mastocytosis.[7] However, the use of aspirin does not always prevent hypotension,[2] flushing[3] and syncopal attacks,[6] and this may be due to levels that are less than therapeutically optimal (< 150 mg/ml).[3]

In the anaesthetic management of patients with mast cell disease, care should be taken to avoid extremes of temperature, trauma to skin and the use of drugs which release histamine. However, it has been suggested that drugs not usually regarded as histamine releasers in normal subjects, may cause mast cell degranulation in patients with high numbers of circulating or tissue mast cells.[8] In such cases, preoperative skin testing would seem sensible.

Premedication with sedative drugs, such as diazepam, is beneficial since stress can precipitate a reaction. However, the most important consideration is probably the continuation of pre-operative sodium cromoglycate, antihistamines and prostaglandin synthetase inhibitors.

Existing reports of anaesthesia for patients who suffer from mast cell disease have shown little risk to the patient[5–7] following the use of a variety of pharmacological agents designed to prevent either degranulation or its effects. Demis[9] reported a four-fold increase in urinary histamine following surgery in a patient who received general anaesthesia for elective saphenous vein surgery. This patient did not suffer related symptoms during the postoperative period and no comment is made on the intra-operative course, which is assumed to have been uneventful. Parris *et al.*[19] recently published brief results that relate to 42 cases of systemic mastocytosis. They encountered only minor complications, more commonly with local anaesthesia than with general, but five patients required adrenaline infusions for the correction of hypotension or bronchospasm. There was no mortality.

In our patient, who had suffered marked acute and chronic complications of mast cell disease, the lack of clinically significant haemodynamic

disturbance and the stability of both histamine levels and thrombin times indicate that mast cell degranulation did not occur. The evidence also suggests that PGD_2 levels were not increased to clinically significant levels. Ideally, histamine should have been assayed from plasma rather than from whole blood, because identification of mast cell degranulation depends on an increase in free circulating histamine, especially in the presence of high numbers of circulating mast cells or basophils. However, our patient had no evidence of mast cell involvement in his peripheral blood and whole blood estimation of histamine would, therefore, have detected tissue mast cell degranulation. It is possible, therefore, that the peri-operative use of sodium cromoglycate may have prevented mast cell degranulation in our patient.

Some authors have advocated the use of preoperative prostaglandin synthetase inhibitors in mastocytosis, but we chose not to do so in our patient for several reasons. Our patient's primary complication of mastocytosis was major upper gastrointestinal haemorrhage. Prostaglandin synthetase inhibitors are known to cause gastric ulceration. Histamine is also a potent stimulator of acid and pepsin secretion, and aspirin has been implicated as a possible trigger for mast cell degranulation. A further concern was the effect of aspirin on platelet numbers and function. The unresolved problems of this patient's possible von Willebrand's disease were also a concern.

This case report and those of others suggest that patients who suffer from mast cell disease and who are to undergo surgery should be adequately stabilised and prepared prior to operation (Table 1). If possible, pre-operative plasma histamine and PGD_2 levels should be measured to give an indication of the predominant vasoactive substance in each patient. Pre-operative therapy with sodium cromoglycate, antihistamines and aspirin should be undertaken unless clinical conditions preclude their use. Management of anaesthesia should avoid the use of histamine-releasing drugs. Cardiovascular monitoring and the measurement of the intra-operative thrombin times and the levels of plasma heparin, histamine and PGD_2, will further aid our understanding of anaesthesia for patients with mast cell disease.

Table 1. Suggested anaesthetic plan for patients with systemic mastocytosis.

Assess systemic involvement of disease process and order appropriate pre-operative investigations, e.g. full blood count, clotting studies, pulmonary function studies.
Measure pre-operative histamine levels and urinary levels of metabolites of PGD_2.
Intradermal skin testing with anaesthetic agents proposed for use.
Continue pre-operative H_1 and H_2 antagonists, prostaglandin synthetase inhibiting agents and sodium cromoglycate.
Sedative premedication, e.g. diazepam.
Consider local or regional anaesthesia if clotting studies are normal.
Avoid histamine-releasing drugs; isoflurane and fentanyl may be anaesthetic agents of choice.
Maintain normothermia.
Take care with blood transfusion (reactions, if they occur, may be severe).
Adrenaline infusion available at all times.
Measure intra-operative haemodynamic data, histamine levels, urinary PGD_2 and clotting studies.

Acknowledgments

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CASE REPORT

Suxamethonium apnoea in a 4-month-old twin

Y. MEHTA AND P. HOLE

Summary

A case of one infant of twins who developed suxamethonium apnoea is described. Investigation of the family revealed him to be homozygous for atypical cholinesterase while the other twin was normal. Tissue HLA and blood typing indicated the twins to be identical.

Key words

Complication; prolonged apnoea.
Enzymes; plasma cholinesterase.

Prolonged apnoea after suxamethonium is due mostly to a genetic variant of plasma cholinesterase but may also be due to low levels of the enzyme or may occur in liver disease,[1] organophosphorous poisoning,[2] malnutrition,[3] hyperpyrexia,[4] burns[5] and myxoedema.[6] We report a case of suxamethonium apnoea due to atypical cholinesterase in one of 4-month-old twins.

Case history

Two 4-month-old male twins, with right-sided inguinal hernias, were to be operated on in the same operating list, one after another.

They were delivered by emergency Caesarean section for premature labour (30 weeks) with bicornuate uterus. The mother received suxamethonium for general anaesthesia without any problems. Twin A weighed 1.5 kg at birth and received nasal continuous positive airway pressure (CPAP) for 24 hours for respiratory distress. Twin B weighed 1.8 kg at birth and was cyanotic. Following intermittent positive pressure ventilation (IPPV) he was found to have a pneumothorax on the right side. This was treated with a chest drain and he was treated with IPPV for 46 hours. Recovery and growth were uneventful and chest X ray and echocardiogram were normal.

Twin A weighed 5.6 kg before planned surgery. He received no premedication. Anaesthesia was induced with oxygen, nitrous oxide and halothane with a Mapleson D (Hafnia) system. A 25-G butterfly-type needle was inserted into the dorsum of the left hand and intravenous atropine 0.1 mg was followed by suxamethonium 5 mg. The patient's trachea was intubated with a 3.0-mm Portex orotracheal tube. Anaesthesia was maintained with oxygen, nitrous oxide, halothane and 2 mg pethidine intravenously. Intra-operatively the child was apnoeic and IPPV was continued manually; the electrocardiogram and rectal temperature were monitored continuously. The procedure lasted for one and a quarter hours and at completion the patient was still apnoeic. Two boluses of naloxone (0.04 mg each) were administered to

Y. Mehta, MD, FFARCS, Senior Registrar, P. Hole, MD, Consultant, Department of Anaesthesia, Odense University Hospital, Sdr. Boulevard, 5000 Odense C, Denmark.

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reverse central depression, if any, due to pethidine. However, this did not have any effect. The child was tested for residual neuromuscular block. There was no twitch or tetanus present even at the maximal voltage and, therefore, a provisional diagnosis of suxamethonium apnoea was made. At this stage the child was flaccid and apnoeic. He was transferred to the postoperative ward and IPPV was continued with a Servo 900C ventilator. The child made a complete recovery after one hour (two and a quarter hours after the administration of suxamethonium). His trachea was extubated and he was transferred to the ward.

Twin B was the next to be operated upon for the same condition. He received 12 mg trimeprazine tartrate (Vallergan) orally 2 hours earlier. He was given atropine 0.2 mg and anaesthesia was induced and maintained with oxygen, nitrous oxide and halothane through a 3-mm Portex orotracheal tube. Suxamethonium was not given. A caudal block was performed with 10 ml 0.125% bupivacaine (plain). Intra- and postoperative periods were uneventful.

The infants and the family were investigated by cholinesterase assays and dibucaine number estimations. The patient with apnoea was found to be homozygous ($E_1^aE_1^a$) for atypical cholinesterase, with low dibucaine number and low serum cholinesterase. He was issued with a warning card and he was registered in the Danish cholinesterase card index.[7] His twin brother was found to be a homozygote with normal cholinesterase and dibucaine number. Both the parents were heterozygotes ($E_1^aE_1^u$). The maternal grandmother was also a heterozygote while the maternal grandfather was a normal homozygote ($E_1^uE_1^u$). The paternal grandmother was heterozygous; the paternal grandfather was dead (Fig. 1).

Plasma cholinesterase assay and dibucaine number determination were performed by the method of Kalow *et al.*[8,9] The erythrocyte phenotyping revealed that both the twins had the same ABO, rhesus, Kell, Duffy, SS, MN, Kidd, Lutheran, P and Lewis blood groups. They also had the same HLA A, B, C, C_c, Ee and MN types. According to these investigations the blood bank reported that they were monozygous twins.

Discussion

The first twin (A) had apnoea for two and a quarter hours after the administration of suxamethonium. In the operating room the absence of any twitch on ulnar nerve stimulation indicated a profound degree of neuromuscular block. The presence of atypical cholinesterase was confirmed by cholinesterase assay and dibucaine number estimation.

The incidence of atypical cholinesterase in the

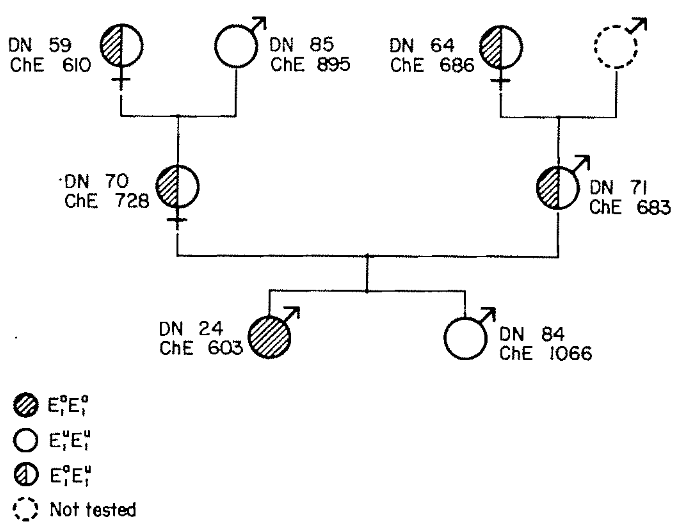

Fig. 1. Genotyping and plasma cholinesterase of the family. Normal values: plasma cholinesterase (ChE), 690–1560 U/litre; dibucaine number (DN), 79–87%.

Danish population is similar to that found in other European countries.[10] Estimation of the dibucaine number is a standard technique for family and population surveys.[11] This revealed a very clear inheritance from both the heterozygous parents.

The presence of atypical cholinesterase has been reported in identical twins[12] but is very rare (1:8000 000). The interesting point about this case is that twin B was homozygous for the usual enzyme and therefore could not be identical (monozygous) with twin A. However, the HLA typing and blood grouping indicated them to be identical, which suggests that the latter forms of typing are non-specific.

Acknowledgment

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CASE REPORT

Miller's syndrome

Anaesthetic management of postaxial acrofacial dysostosis

M. RICHARDS

Summary

A new case of Miller's syndrome is reported and the characteristic features are described along with a brief outline of related conditions. The anaesthetic management is discussed and the problems which may be encountered when dealing with this syndrome are highlighted.

Key words

Complications; Miller's syndrome.
Intubation, tracheal; difficult.

The syndrome of postaxial acrofacial dysostosis was first described as a complete clinical entity by Miller in 1979.[1] At that time there were six recorded cases, and few have been added to the literature since. The syndrome comprises craniofacial abnormalities similar to those of the Treacher–Collins syndrome but associated with upper and lower limb defects mainly on the postaxial side of the limb (Fig. 1, Table 1). There are several closely related syndromes of acrofacial dysostosis (AFD)[2,3] (Table 2). No previous reports of the anaesthetic management of patients with Miller's syndrome were found.

Table 1. Miller's syndrome: recognised features.

Craniofacial
Malar hypoplasia
Micrognathia
Cleft lip and/or palate
Ectropion
Absent superior orbital ridges
Hypoplastic ears
Limbs
Postaxial deformities (i.e. ulnar aspect)
Absence of 4th and 5th rays in hands and feet
Shortening of limbs
Cardiac
Defects, e.g. ASD, VSD and patent ductus arteriosus
Mental development
Normal intelligence usual
Other stigmata
Accessory nipples

Case history

The patient was delivered by Caesarean section for failure to progress and was noted at birth to have gross physical abnormalities, which were identified as belonging to Miller's syndrome. She did not have any cardiac abnormalities.

She presented for repair of cleft palate at the age of 12 months. She had been anaesthetised for corrective surgery for severe bilateral ectropion at the age of 4 weeks, at which time it had been noted that tracheal intubation was difficult. Unfortunately, the lids still did not protect the eyes.

Clinical examination revealed a 7.7-kg child

M. Richards, MB, BCh, FFARCS, Consultant, Middlemore Hospital, Otahuhu, Auckland 6, New Zealand.

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Fig. 1. Lateral view of the head of the patient aged 4 weeks. Note the Treacher–Collins-like features.

Fig. 2. The patient aged 12 months. Note the abnormal development of the face. The 4th and 5th rays of the hands are absent and the limbs are shortened and require splinting.

Table 2. Related or similar syndromes.

Acrofacial dysostosis (AFD)
Miller's AFD
  See Table 1
Nager AFD
  Malar hypoplasia
  Cleft palate
  Pre-axial limb defects
Split foot AFD
  Retro-micrognathia
  Cleft palate
  Split feet (normal upper limbs)
Distal-2q AFD*
  Micrognathia
  Abnormalities mainly confined to limbs
Cardiomelic AFD
  Hemifacial microsomia
  VSD

Mandibulofacial dysostosis (MFD)
Treacher–Collins MFD
  Malar and mandibular hypoplasia
  Cleft palate
  Congenital heart defects

* Duplication of the distal 2q chromosome.

with normal mental development but severe physical abnormalities. The most important to the anaesthetist were a relatively large head, malar hypoplasia, micrognathia, cleft palate and shortened limbs (Fig. 2). It was noted that particular care would have to be taken of the eyes, as the lids did not cover the cornea at all. A second anaesthetist was requested for the case because of the possibility of a difficult induction and intubation.

Premedication with droperidol 0.15 mg and atropine 150 μg was given 1.5 hours pre-operatively. She was calm and slightly drowsy on arrival for surgery, and this allowed intravenous access to be established prior to induction without distress. The cannula was placed in the left foot because of the paucity of developed veins at any other site. Previously, intravenous cannulation had been successful only in scalp veins. Electrocardiograph monitoring was established and a precordial stethoscope attached.

Gaseous induction with halothane in 100% oxygen was then undertaken using a non-rebreathing system with reservoir bag. The fit of the mask was poor because of the facial abnormalities and a seal was achieved only by

the use of two hands. Complete obstruction of the airway occurred as the depth of anaesthesia increased and this was relieved only partly by the use of an oral airway and careful positioning of the head and neck. A nasal airway was considered but rejected because assisted ventilation became possible shortly afterwards.

At this time suxamethonium 1.5 mg/kg was administered and ventilation continued by hand. Laryngoscopy did not reveal the cords, although the posterior aspect of the arytenoids could just be seen. A small gum-elastic introducer was manipulated blindly into the trachea with some difficulty and a non-cuffed Oxford orotracheal tube (size 3.5 mm) was inserted over this and guided into place. The eyelids were taped carefully so as to cover the eyes and prevent desiccation of the corneas.

Anaesthesia was maintained with nitrous oxide 60% in oxygen, supplemented by halothane, during which the child breathed spontaneously. The cleft palate was repaired without problem and a tongue stitch was inserted to allow forward traction on the tongue during recovery. A nasopharyngeal airway could not be passed into either nostril prior to extubation, due to undiagnosed choanal atresia. Both sides were forcibly dilated using gum-elastic bougies and artery forceps, and the airway was positioned without further problem.

Extubation was accomplished while the patient was deeply anaesthetised but with adequate spontaneous ventilation. The immediate postoperative period in the recovery room was uneventful and the infant was returned to the ward with special nursing cover. Three episodes of significant partial respiratory obstruction were noted during the following 18 hours, and all were relieved by gentle support of the jaw by the attending nurse. Subsequent progress was uneventful.

Discussion

The striking feature of Miller's syndrome is the grossly abnormal physical development with normal intelligence. The normal mental development makes cosmetic intervention important and rewarding. Normal psychological development is to be encouraged and, therefore, a normal physical appearance is the desired end point to surgical intervention.

Patients with Miller's syndrome therefore present early for a course of plastic surgery which may last several decades. The anaesthetist must take time to establish a good rapport and consider the best anaesthetic approach to a child who will present for multiple interventions.

Pre-operative assessment is important in order to establish the degree of abnormality. Malar hypoplasia, micrognathia and cleft palate imply possible pre- and postoperative respiratory obstruction as well as a poor mask fit and difficult intubation. Similar problems are encountered with Treacher–Collins syndrome.[4,5] In this case, a premedication was chosen which would not produce deep sedation and thereby compromise the airway. A gaseous induction was felt to be the safest approach; however, the airway was difficult to manage during induction. When it was established that manual ventilation could be achieved, it was considered that the risks of neuromuscular blockade with suxamethonium were minimised and that relaxation would produce optimum intubation conditions. Pre-operative tracheostomy has been suggested for difficult intubation in the Treacher–Collins syndrome.[6] However, this does not appear to be appropriate in Miller's syndrome unless intubation is impossible by other means, as multiple anaesthetics are likely to be required over a 10–20-year period.

Limb shortening and deformity resulted in two areas of difficulty in this case. One was patient positioning, as the limbs required extra support in the supine position to prevent stress on the joints and neighbouring neurovascular structures. The other was the dearth of reasonable limb veins for intravenous access; it was also difficult to secure the cannula in place.

Choanal atresia has not been described previously in Miller's syndrome and should be excluded before anaesthesia. The bleeding from attempted nasal intubation could have resulted in complete respiratory obstruction prior to intubation. It was fortunate that a nasal airway was not required during induction.

Cardiac abnormalities should always be sought before anaesthesia is started. Those associated with Miller's syndrome are atrioseptal defects, ventriculoseptal defects and patent ductus arteriosus. When patients with a possible right-to-left shunt are anaesthetised, extra care should be taken to avoid air bubbles in the intravenous fluid because of the risk of cerebral embolus.

Conclusion

The postaxial acrofacial dysostosis (Miller's) syndrome is comprised of Treacher–Collins-like facies with abnormal limb development. One important aspect of the condition is that these children are usually of normal intelligence.

The main problems which may be encountered by the anaesthetist are difficult intubation and airway management, poor intravenous access, the need for support for the limbs of the anaesthetised child and the possibility of cardiac abnormalities.

The other related acrofacial dysostosis syndromes may present similar problems that depend on the associated abnormalities and the degree of involvement.

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CASE REPORT

Spontaneous retrobulbar haemorrhage following anaesthesia

K. E. J. GUNNING AND B. J. COLLETT

Summary

A case is presented of retrobulbar haemorrhage following anaesthesia for the removal of a chicken bone from the pharynx of a patient with systemic lupus erythematosus. The aetiology and treatment are discussed.

Key words

Complications; retrobulbar haemorrhage.

Accepted anaesthetic practice for patients with a full stomach includes extubation with intact laryngeal reflexes. In these circumstances it is difficult to avoid the patient coughing during tracheal extubation. This may cause high venous pressures and lead to congestive haemorrhage in susceptible patients. Retrobulbar haemorrhage may rarely be caused by this increase in pressure. This complication has not previously been reported after general anaesthesia and this case is reported to draw attention to the clinical signs, since early diagnosis may be important in the management of the condition.

Case history

A 51-year-old female was admitted with a chicken bone lodged in her pharynx. Three years previously a diagnosis of systemic lupus erythematosus (SLE) was made. She was asymptomatic and receiving no medication at the time of admission, and there was no past history of spontaneous bruising or bleeding. There were no abnormal findings on examination, apart from the facial rash characteristic of SLE. Rapid sequence induction of anaesthesia was performed since she had a full stomach. After preoxygenation for 5 minutes and the application of cricoid pressure, anaesthesia was induced with thiopentone 250 mg. Suxamethonium 100 mg was given to facilitate tracheal intubation. Her eyes were closed with adhesive tape. During the procedure the patient's lungs were ventilated with 30% oxygen in nitrous oxide and halothane 0.75%. Atropine 600 μg and a further 20 mg of suxamethonium were given. After uneventful removal of the chicken bone she was turned on her left side, tipped 15° head down and extubated when her laryngeal reflexes had returned. She had a short episode of coughing as the tracheal tube was removed. In the recovery area her left eye was noted to be slightly red and puffy. Two hours later the eye was painful, obviously swollen and she complained of diplopia on medial and lateral gaze. Ophthalmic examination revealed normal visual acuity in both eyes. There was a 6-mm proptosis of the left eye with downward displacement, chemosis, but no vas-

K.E.J. Gunning, FRCS, FFARCS, B.J. Collett,* MB, BS, FFARCS, Senior Registrars, Department of Anaesthesia, Kings College Hospital, Denmark Hill, London SE5 9RS.
* Now Consultant Anaesthetist, Whipps Cross Hospital.

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cular engorgement of the conjunctiva. Fundoscopy revealed mild engorgement of the retinal veins. She was unable to elevate the eye and adduction, abduction and depression were limited. Examination of the right eye was normal. A diagnosis of retrobulbar haemorrhage was made and the diagnosis confirmed by computerised axial tomography scan. Full blood count yielded the following results: haemoglobin 13.4 g/dlitre, white cell count 4.5×10^9/litre, platelets 110×10^9/litre; clotting studies were normal and the ESR was 35 mm/hour. Antinuclear factor was positive at 1:20 and DNA binding significantly elevated at 54.0; levels of C_3 and C_4 were low at 0.43 and 0.11 g/litre, respectively. She was treated conservatively with bed rest alone and her eye improved as the haematoma resolved. She was discharged from hospital 5 days later with only a mild proptosis of 3 mm. One month later she was asymptomatic and the left eye was normal.

Discussion

Retrobulbar haemorrhage is an uncommon condition which usually occurs in association with malar or ocular trauma, or following a retrobulbar block. Spontaneous haemorrhage can occur in a fit individual[1] or in association with haemophilia[2] and blood dyscrasias.[3] Congestive haemorrhages due to venous engorgement rarely occur as the orbital venous plexus has many exits, draining via the superior and inferior ophthalmic veins into the cavernous sinus. This drains into the jugular vein via the superior and inferior petrosal sinuses.[4] Widespread congestion in this valveless system is necessary to give rise to sufficient pressure to cause a retrobulbar haemorrhage. Haemorrhage in this situation has been reported after strangulation,[3] external cardiac massage,[5] and during the second stage of labour.[6] The clinical features are orbital pain, decreased visual acuity, proptosis and pallor of the optic disc. Permanent blindness is rare and is probably due to a neuropathy of the optic nerve secondary to compression or ischaemia.[7] It may occur if the diagnosis is not made early and treatment instituted. The diagnosis can usually be made on the clinical findings and confirmed by computer tomography or ultrasound of the orbit. Treatment is conservative with bed rest, ice packs and diuretics. Surgical decompression must be performed if there is increasing proptosis or deterioration of visual acuity.

In our patient it is unlikely that her SLE contributed to the haemorrhage as, although the platelet count was low, it was above that at which spontaneous haemorrhage usually occurs. She had no evidence of impaired coagulation due to lupus anticoagulant or factor VIII antibody, which are seen in SLE. The haemorrhage was probably caused by a sudden widespread elevation of venous pressure when the patient coughed as the tracheal tube was withdrawn at extubation. In addition, the head-down tilt of the patient at extubation would have increased venous pressure. However, the patient may have had an underlying congenital venous malformation as reported by Krohel *et al.*[6] This explains the occurrence of recurrent haemorrhages and may be the reason why they are not seen more frequently in similar situations. The most important aspect of the condition is early diagnosis so that a decompression may be performed, if necessary, to prevent permanent blindness.

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Anaesthesia, 1987, Volume 42, pages 877–878

APPARATUS

A new laryngoscope

A modified laryngoscope to facilitate intubation in cases of restricted access

G. NUNN

Summary

This is a report of a modification to one design of laryngoscope to increase the angle between blade and handle, to facilitate intubation in cases of difficult access, such as in obstetric practice or in patients in whom neck flexion is limited, for example by skull traction. The modification offers the unique advantage of two useful blade angles in one instrument. The first type described would be suitable for use in small units where it is thought that a laryngoscope solely for use in rare cases of difficult access would not be justified. It would also be suitable for inclusion in resuscitation kits for use both within and outside hospital. The second type would be more suitable for the maternity or spinal injuries unit, or the difficult intubation box of a general operating theatre suite.

Key words

Equipment; laryngoscope.
Anaesthesia; obstetric, spinal injury, intubation.

Failed tracheal intubation remains high on the list of causes of maternal death.[1,2] The application of cricoid pressure can present a considerable handicap to easy insertion of the laryngoscope in such cases and, indeed, in a wider range of emergency work, where mortality and morbidity are not so adequately recorded. Restricted access may also be a problem in cases of fixed neck flexion or where external fixation apparatus obstructs the easy movement of the laryngoscope handle. Various authors have described modifications to standard laryngoscopes to ease insertion in such cases of difficult access. These have been based upon an angled insert to fit between blade and handle,[3] or on a modified blade such as the Polio blade and that described by Kessell.[4]

It has been the author's experience that the Polio blade is both straighter than is needed for the overwhelming majority of cases of restricted access, and is awkward to use. It was therefore my intention to produce a design that was not significantly harder to use than the standard Macintosh pattern. All these modifications are based upon the Penlon version of the Macintosh laryngoscope. The use of the Medical and Industrial Equipment (M&IE) version allows one blade and handle to provide two different angles by the simple expedient of reversing the blade, which is not possible with the Penlon instrument.

Description of the modification

The angle of the M&IE laryngoscope is set by the abutment of a projection on the hinge block against a machined surface on the handle. This surface is normally perpendicular to the axis of

G. Nunn, FFARCS, Consultant, Pinderfields General Hospital, Aberford Road, Wakefield, West Yorkshire.

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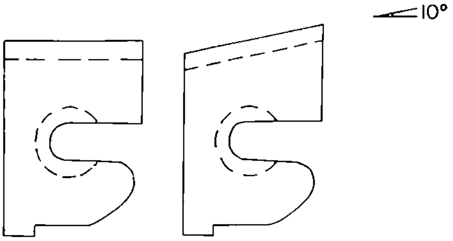

Fig. 1. Hinge blocks. Standard and modified type one.

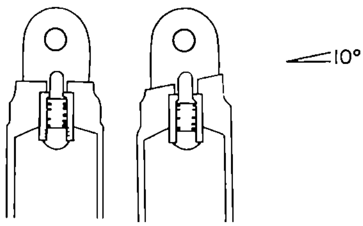

Fig. 2. Handles. Standard and modified.

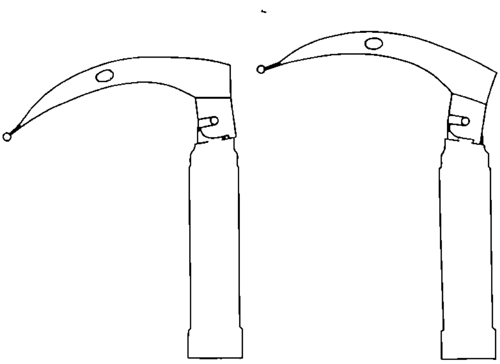

Fig. 3. Type one modified laryngoscope in standard and plus 20° positions.

the handle. The modified instrument has this surface built up on one side and then machined at an angle of 10°. Thus, if the blade is removed and replaced with the handle rotated by 180°, the angle of handle to blade will be changed by 20°.

The first type has a modified hinge block which gives a 10° increase in angle. Thus the combination of the modified blade and handle gives either the standard or a plus 20° angle (Figs. 1–3).

This first version found favour amongst colleagues of all grades in obstetric practice. However, it became clear that, due to a plentiful supply of standard laryngoscopes, it was being used only in the plus 20° position. A second blade was therefore made with an 18° increase in hinge-block angle so that the two blade angles are plus 8° and plus 28° when used with the modified handle. Choice of a suitable blade thus allows a combination of standard and increased angle, or two increased angles.

Discussion

Two versions of a novel modification to a Macintosh laryngoscope have been described. Type one offers normal and plus 20° angles, suitable for use where a standard instrument is not readily available. Type two offers two increased angles; in the current prototype, these are plus 8° and plus 28°. This instrument is more suitable for use where standard laryngoscopes are readily available.

These instruments offer a unique advantage over previously described modifications in that the one laryngoscope offers two different angles. The change from one angle to the other takes about 8 seconds to perform. Those who have used the first prototype in the plus 20° position have reported it to be no harder to manipulate than the standard instrument, and yet greatly to facilitate insertion of the blade.

Acknowledgments

I would like to thank Mr R. Hall, Mr B. Bailey and the Department of Medical Illustration at Coventry and Warwick Hospital for their advice and assistance.

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Anaesthesia, 1987, Volume 42, pages 879–882

Forum

Arterial oxygen saturation during general anaesthesia for paediatric dental extractions

M. E. Bone, MB, ChB, FFARCS, D. Galler, MB, BS, Registrars, Department of Anaesthetics, The London Hospital, Whitechapel, London, P. J. Flynn, MB, FFARCSI, DCH, DObst, Senior Lecturer, Anaesthetic Unit, The London Hospital Medical College, Whitechapel, London.

Summary

Arterial oxygen saturation (Sa_{O_2}) was measured in 50 healthy children undergoing dental extractions under general anaesthesia. An inhalational anaesthetic technique was employed, with an inspired oxygen concentration of 33%. There were decreases in Sa_{O_2} of greater than 5% of the baseline value in 70% of patients, and greater than 10% in 26% of patients. The majority of these decreases were associated with teeth extractions or during placement of dental prop and pack. Non-Caucasion children showed a significantly ($p < 0.05$) greater maximum decrease in Sa_{O_2} from baseline value compared to Caucasian children. The maximum decreases in Sa_{O_2} from baseline value in children anaesthetised by supervised dental students, and in children whose extractions were performed by dental students, were significantly ($p < 0.05$) greater than in children whose anaesthetic and surgery were performed by members of staff.

Key words

Anaesthesia; paediatric.
Measurement techniques; oximetry.

General anaesthesia is widely practised for outpatient dental extractions in children in the United Kingdom. Dental students at The London Hospital Dental Institute are required to administer general anaesthesia to these patients as part of their undergraduate training, under the direct supervision of an anaesthetic consultant or senior registrar.

Previous studies[1] have shown decreases in oxygen saturation in excess of 5% in adults who received inspired oxygen concentrations of 20, 25 or 30%, when anaesthesia was administered by dental undergraduates. Decreases in oxygen saturation in excess of 10% have been reported[2] in paediatric patients who received an inspired oxygen concentration of 30%, after intravenous induction of anaesthesia.

The purpose of the present study was to measure oxygen saturation in children who presented for outpatient dental extractions using an inhalational anaesthetic technique, with an inspired oxygen concentration of 33%.

Patients and methods

Arterial oxygen saturation (Sa_{O_2}) was measured in 50 children, ASA grade 1, undergoing outpatient dental extractions under general anaesthesia at The London Hospital Dental Institute. Anaesthesia was administered by an anaesthetic consultant, senior registrar or registrar, or by a fourth- or fifth-year dental student under direct supervision. The extractions were undertaken by a senior registrar or registrar in oral surgery, or by a supervised dental student. The Sa_{O_2} readings were recorded by an independent observer, using a BTI Biox III Ear Oximeter (Ohmeda).

Induction of anaesthesia. The patient was supine on an operating table and the ear probe was placed on the ear lobe. A baseline reading of arterial oxygen saturation was obtained for 2 minutes. Subsequent readings were recorded from the continuous digital display at 30-second intervals. All patients were monitored with lead II of a three-lead electrocardiogram (ECG). A gaseous induction was performed using nitrous oxide in oxygen with an inspired oxygen concentration of 33% (F_{IO_2} 0.33). Nitrous oxide was supplemented with halothane from a Fluotec Mark III vaporizer (Cyprane), in concentrations of up to 3%. The anaesthetic apparatus employed was a standard Boyle's machine, a Bain system and a Goldman nasal mask with its expiratory valve closed. The fresh gas flow was at least twice the patient's estimated minute volume, and never less than 3 litres/minute.

Surgery. When depth of anaesthesia was judged to be adequate, the operator was allowed to insert a Devonshire mouth prop and an oropharyngeal pack of 7.5 cm wide gauze. The teeth were then extracted. The pack and prop were removed at the end of the procedure and the patient was turned into the lateral position.

Statistical analysis of the results was carried out using an unpaired Student's *t*-test.

Results

The patients' demographic data are shown in Table 1. Thirty-five patients were Caucasians, eleven were Asians and four were sickle-negative West Indians. Twenty-five patients were anaesthetised by members of the anaesthetic department, and the remainder by supervised dental students. Sixteen patients had teeth extracted by supervised dental students and 34 by an oral surgical registrar or senior registrar.

Table 1. Patient demography.

	Mean (SEM)	Range
Age, years	6.30 (0.48)	2–16
Number of teeth extracted	3.10 (0.35)	1–12
Duration of anaesthesia, minutes	6.80 (0.44)	3.5–19

The mean baseline $Sa\text{O}_2$ in air, and the lowest reading of $Sa\text{O}_2$ noted during inspiration of 33% oxygen, are presented in Table 2. The record for each patient was examined for any decrease in oxygen saturation greater than 5% or greater than 10% of the baseline value (i.e. a decrease to less than 95% or less than 90% of control). The lowest level of oxygen saturation reached during these decreases was noted.

Table 2. Arterial oxygen saturation.

	Mean % (SEM)	Range
Baseline $Sa\text{O}_2$ in air	97.50 (0.27)	93–100
Lowest recorded $Sa\text{O}_2$ with $F\text{IO}_2$ 0.33	90.80 (0.65)	77.2–100
Maximum percentage decrease in $Sa\text{O}_2$ from baseline	6.70 (0.67)	0–21.4

In 15 of the patients there were no episodes in which $Sa\text{O}_2$ decreased by more than 5%. Twenty-two patients were found to have decreases in $Sa\text{O}_2$ of between 5 and 10%, and 13 patients showed decreases of greater than 10% of the baseline value. The mean maximum decrease (MMD) in $Sa\text{O}_2$ from baseline value was 6.7% (SEM 0.67). The histogram in Fig. 1 shows the lowest levels of $Sa\text{O}_2$ reached. The duration of decreases in $Sa\text{O}_2$ which exceeded 10% of control, was in all cases less than 2 minutes. Factors associated with the lowest $Sa\text{O}_2$ readings are shown in Table 3.

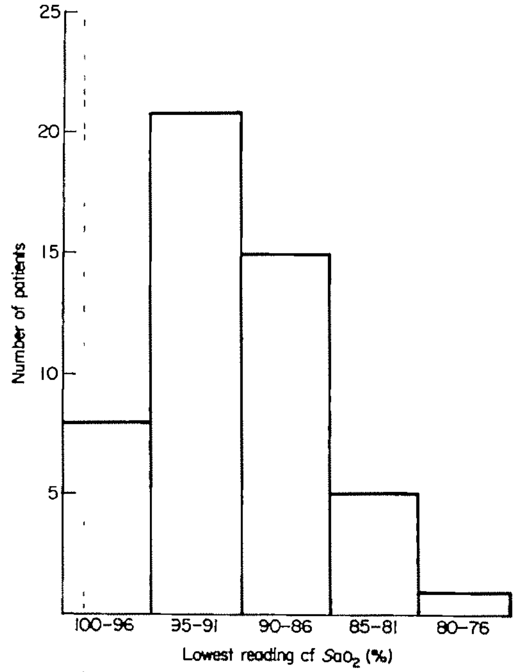

Fig. 1. Histogram of lowest readings of $Sa\text{O}_2$.

Table 3. Procedures associated with maximum decreases in $Sa\text{O}_2$.

Factors	Number of patients*
Induction	1
Insertion of prop and pack	10
Examination of teeth	1
Changing sides with prop	4
Extractions	28

* Excluding six patients with no decrease in $Sa\text{O}_2$ from baseline.

There was a significant difference ($p < 0.05$) between the MMD in $Sa\text{O}_2$ in the 15 non-Caucasian children compared with the 35 Caucasian. A significant difference ($p < 0.05$) was found between the MMD in $Sa\text{O}_2$ in those children anaesthetised by anaesthetists compared to supervised dental students. The MMD in $Sa\text{O}_2$ in children whose extractions were performed by an oral surgeon, was significantly less than that when extractions were undertaken by a supervised dental student (Table 4).

No correlation could be demonstrated between age of patient and the lowest readings of $Sa\text{O}_2$. There was a trend for procedures of longer duration to be associated with greater decreases in $Sa\text{O}_2$, although this did not reach statistical significance.

In four patients, ventricular ectopic beats were noted on the ECG during anaesthesia. In three instances these were associated with decreases in $Sa\text{O}_2$ from baseline of over 10%, and occurred during dental extractions. In the fourth case, ectopic beats occurred

Table 4. Factors associated with maximum decreases in Sa_{O_2}.

	Mean (SEM) maximum decrease in Sa_{O_2}, %
Non-Caucasian patients (n = 15)	9.0 (1.5)
Caucasian patients (n = 35)	5.8 (0.6)
Anaesthesia by anaesthetist (n = 25)	5.5 (0.8)
Anaesthesia by dental student (n = 25)	8.1 (1.0)
Extractions by oral surgeon (n = 34)	5.5 (0.7)
Extractions by dental student (n = 16)	9.3 (1.3)

during induction of anaesthesia, when Sa_{O_2} was 96.8%. Only one patient appeared clinically to be cyanosed; this was a 4-year-old Asian girl undergoing extraction of six teeth. Both anaesthesia and surgery were performed by supervised dental students, and the lowest recorded Sa_{O_2} was 77.2%, a decrease of 21.4% in comparison with the baseline value.

Discussion

This study investigated the oxygenation of children undergoing dental extractions using an inhalational technique and an F_{IO_2} of 0.33. The results show decreases in Sa_{O_2} of greater than 5% of the baseline value in 70% of patients, and greater than 10% in 26% of patients. The mean lowest recorded Sa_{O_2} was 90.8%. Such a value represents a Pa_{O_2} of approximately 8 kPa, assuming normocapnia and a temperature of 37.4°C. Levels lower than this were recorded in 50% of the children. Such decreases in oxygenation represent a significant degree of hypoxia.

Hypoxia during general anaesthesia is still considered to be one of the major complications during dental anaesthesia and has been identified as a major threat to life.[3] Over 50% of the anaesthetic-related deaths were associated with respiratory complications in Coplans and Curson's review[4] of deaths associated with dentistry for the 10-year period 1970–79.

A previous study[2] of oxygen saturation during dental anaesthesia in children of a similar age which used an F_{IO_2} of 0.3, showed over 50% of the patients to have readings of Sa_{O_2} below 90%. This is similar to our findings. In another study,[1] only five out of 23 patients (22%) had an Sa_{O_2} of 90% or below, when the inspired oxygen concentration was 30%. This latter study predominantly investigated adults. The higher incidence of low Sa_{O_2} in children may suggest that greater vigilance is required for respiratory complications in younger patients. The mean age of patients whose deaths were associated with general anaesthesia in hospital outpatients in the period 1970–79 was 11.75 years.[4]

The paediatric patient is at particular risk from respiratory complications during general anaesthesia. Metabolic rate and alveolar minute volume are greater than in the adult, whilst functional residual capacity is a similar fraction of lung volume. Consequently, changes in depth of anaesthesia and hypoxia occur more rapidly in the child. The small airway and relatively large tonsils and adenoids may lead to airway obstruction under anaesthesia. Airway control and recognition of obstruction remain two of the most difficult manoeuvres to teach trainee anaesthetists. During this study, obstruction of the airway was the most common cause of a decrease in Sa_{O_2}.

We found a significantly greater incidence of Sa_{O_2} decrease in non-Caucasian children compared to Caucasian children. A previous study[2] indicated marked decreases in Sa_{O_2} that occurred in two non-Caucasian children. Such findings are difficult to explain, although the recognition of hypoxia by clinical cyanosis is less obvious in dark skinned patients. Lunn and Mushin, in their report[5] on mortality associated with anaesthesia, suggest that the need for increased vigilance in these patients is still not sufficiently appreciated by some anaesthetists.

Greater decreases in Sa_{O_2} were associated with both student anaesthetist and student operator, but decreases in Sa_{O_2} did occur with all grades of anaesthetist and operator. Similar decreases in Sa_{O_2} in children have been recorded when anaesthesia was undertaken only by anaesthetists.[2] Thornton[6] has postulated that a degree of airway obstruction may be inevitable during dental extractions, even with experienced personnel. It would appear prudent to avoid the combination of student anaesthetist and student operator.

The majority of decreases in Sa_{O_2} in our study occurred during dental extractions, or during insertion of prop and pack. Negligible decreases in Sa_{O_2} were recorded at induction of anaesthesia. Hypoxia was caused by respiratory obstruction in 20% of adult patients at the time of insertion of the prop or pack and during dental extractions, in a study which used an inhalational technique with an F_{IO_2} of 0.3.[7] This is in contrast to the findings of Beeby and Thurlow[2] in their evaluation of a pulse oximeter in children during anaesthesia for dental extractions. The decreases in Sa_{O_2} mostly occurred at induction immediately following intravenous methohexitone, although some decreases in Sa_{O_2} were related to placement of prop and pack, or during adjustment of the nasal mask. An inhalational technique may therefore offer safer anaesthesia for children.

Our findings suggest that an inhalational anaesthetic technique for dental extractions in children avoids the decreases in Sa_{O_2} associated with intravenous induction but, despite an F_{IO_2} of 0.33, a significant degree of hypoxia occurred in 50% of the children.

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Anaesthesia, 1987, Volume 42, pages 882–884

The influence of premedication on the occurrence of dysrhythmias during oral surgery

D. C. Smith,* BMedSci, BM, BS, FFARCS, Registrar, Department of Anaesthesia, P. O'Connell, Technician, Cardiac Department, University College Hospital, Gower Street, London WC1E 6AU.

Summary

The incidence of cardiac dysrhythmia during inpatient dental anaesthesia with enflurane was studied following either hyoscine or droperidol as a supplement to papaveretum premedication. None of the subgroup given droperidol exhibited dysrhythmias, compared to 4.4% of those patients given hyoscine. This difference was not significant at the 5% level $(0.2 > p > 0.1)$.

Key words

Complications; dysrhythmia.
Premedication; droperidol, hyoscine.

Dysrhythmias are common following stimulation of the trigeminal nerve during oral surgery.[1] The incidence of dysrhythmias during enflurane anaesthesia is known to be less than that exhibited under halothane anaesthesia.[2,3] We have previously reported that, during halothane anaesthesia, the incidence of dysrhythmias following hyoscine premedication is higher than that following droperidol premedication.[4] The present study was designed to determine whether the same effect could be demonstrated with enflurane.

Methods

One hundred and thirty-four patients scheduled for dental extractions, primarily of impacted third molars, were studied. All patients were ASA grade 1.

The investigation was conducted as reported previously.[4] Briefly, randomly allocated premedication of papaveretum 10–20 mg, combined with either hyoscine 0.2–0.4 mg or droperidol 2.5–7.5 mg, was administered 60–90 minutes prior to induction of anaesthesia. All anaesthetics were administered by the author with the help of the same operating department assistant. A standard induction sequence was employed, which consisted of thiopentone 5 mg/kg, suxamethonium 1 mg/kg and tracheal intubation under direct vision with a nasotracheal tube. Spontaneous ventilation was allowed to resume with a Mapleson A system that delivered a fresh gas flow of 100 ml/kg/minute. Anaesthesia was maintained with 33% oxygen in nitrous oxide, supplemented with enflurane 3% inspired concentration for 5 minutes, reduced to 2% thereafter. During surgery the electrocardiogram (ECG) was recorded continuously onto cassette tape. The coded tapes were subsequently analysed double-blind for dysrhythmias, in the cardiac department. Results were analysed for statistical significance using the Chi-squared test; Yates' correction for continuity was applied.

* Correspondence should be addressed to Dr D.C. Smith, Instituut voor Anesthesiologie, Sint Radboud Ziekenhuis, Postbus 9101, 6500 HB Nijmegen, The Netherlands.

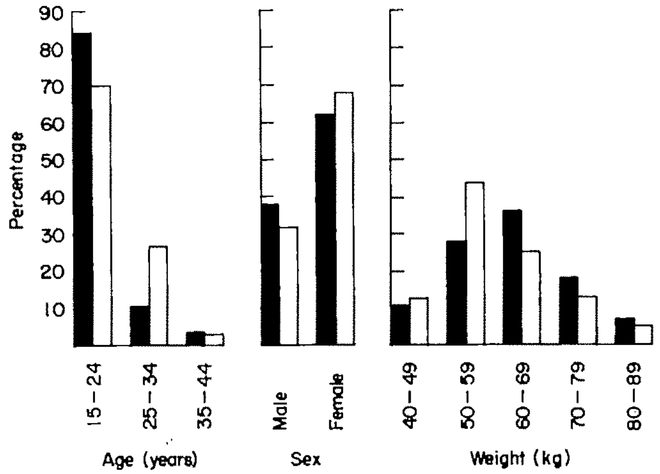

Fig. 1. The percentage distribution of age, sex and body weight between the two study groups. ■, Hyoscine; □, droperidol.

Table 1. Distribution of the different dysrhythmias between the two study groups.

	Papaveretum with hyoscine	Papaveretum with droperidol
Unifocal ventricular ectopic	1	—
Unifocal bigemini	2	—
Total	3	0

Results

The study groups were comparable in terms of age, sex and weight distribution (Fig. 1). The dysrhythmias exhibited are shown in Table 1. The subgroup who received droperidol exhibited no dysrhythmias in comparison to three (4.4%) of the patients who received hyoscine, but this difference was not statistically significant ($0.2 > p > 0.1$).

Discussion

The incidence of cardiac dysrhythmias reported here for the hyoscine subgroup is similar to that reported in other studies.[2,3] The high incidence of cardiac dysrhythmias following the use of halothane in combination with an anticholinergic agent, probably results from the interplay of two phenomena. Firstly, a reduction in the refractory period[5] and conduction times[6] of the atrioventricular (AV) node associated with anticholinergic agents, produces a situation in which initiation of re-entry dysrhythmias is facilitated.[1] Secondly, in the presence of high catecholamine levels, halothane allows the emergence of ectopic AV nodal or ventricular foci.[7,8] All inhalational anaesthetics in current use may indirectly prolong AV nodal[5,6] and His-Purkinje[6] conduction times, but enflurane does not have the same capacity as halothane for the production of myocardial sensitivity to catecholamines.[8] The subtle interaction between volatile anaesthetics and anticholinergic agents to produce variable conduction blockade in the AV-nodal–His-Purkinje system, may facilitate the generation of re-entry dysrhythmias. However, an asynchronous beat or ectopic focus in the conducting system seems to be the important requirement for initiation of these dysrhythmias, although aberrant conduction may be responsible for their propagation. This may explain the high incidence of cardiac dysrhythmias seen under halothane anaesthesia as compared to anaesthesia with enflurane.

Acknowledgments

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Intranasal nitroglycerine attenuates pressor response to tracheal intubation in beta-blocker treated hypertensive patients

V. K. Grover, MD, MNAMS, Assistant Professor, S. Sharma, MD, Lecturer, R. P. Mahajan, MD, Senior Resident, H. Singh, MS, DA, MAMS, Professor, Department of Anaesthesia, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Summary

The effect of intranasal nitroglycerine on the pressor response to laryngoscopy and tracheal intubation was studied in 40 adult hypertensive patients treated with beta-blocking drugs. Nitroglycerine 0.75 mg, administered intranasally 30 seconds before induction of anaesthesia, was compared with a placebo solution of saline. Haemodynamic variables were measured for 10 minutes after laryngoscopy and tracheal intubation. Heart rate did not change significantly in either group. Systolic as well as mean arterial blood pressure increased significantly for the first 5 minutes in the control group, whereas patients in the nitroglycerine group showed a decrease in systolic as well as in mean arterial pressure. No patient in the nitroglycerine group showed a decrease in systolic arterial pressure greater than 20 mmHg. In conclusion, intranasal nitroglycerine ameliorates the pressor response to laryngoscopy and tracheal intubation in beta-blocked patients.

Key words

Anaesthetic techniques; tracheal intubation.
Pharmacology; nitroglycerine.

Tachycardia and hypertension are well-documented reflex cardiovascular effects of laryngoscopy and tracheal intubation in normotensive subjects.[1] The extent of these reflexes is more marked in both treated and untreated hypertensive patients.[2] Intranasal nitroglycerine has been shown to attenuate the pressor response to laryngoscopy and intubation in normotensive patients.[3] Its use in hypertensive patients has not been reported so far. The present study was undertaken to assess the effect of nitroglycerine solution administered intranasally before laryngoscopy, to prevent the cardiovascular changes associated with laryngoscopy and tracheal intubation.

Material and methods

The study was carried out in a double-blind manner. Forty, mild to moderately hypertensive patients (pretreatment diastolic arterial pressure 100–130 mmHg) receiving therapy in the form of beta-blocking drugs alone, or in addition to a diuretic, were selected. Patients with obstructive lung disease, a history of angina or previous myocardial infarction, congestive cardiac failure or 2nd and 3rd degree AV block, were excluded from the study. All the patients were scheduled for short surgical procedures.

The day before surgery, the purpose of the study and the procedure to be undertaken were explained to the patients and informed consent was obtained. The antihypertensive medication was continued until the morning of surgery. All the patients were placed first on the operation list, so that the interval between the morning dose of antihypertensive medication and induction of anaesthesia was about 2 hours. Premedication was with morphine 0.1 mg/kg and promethazine 0.4 mg/kg intramuscularly, one hour before anaesthesia. Patients were allocated to one of two groups (20 in each group) with the help of a randomisation chart.

The arterial blood pressure was measured after a resting period of 10 minutes, subsequent to arrival of

the patient in the operating theatre. Basal heart rate readings were recorded after a continuous display of heart rate and ECG had been established on an oscilloscope using ECG leads in the CM5 position. Depending upon the allocation of patients to a particular group, they received either 1.5 ml normal saline (group 1) or 1.5 ml nitroglycerine solution (group 2). The nitroglycerine solution was prepared by dissolving two crushed tablets of 0.5 mg each in 2 ml saline, by a worker who was not associated with the monitoring of blood pressure and heart rate. The same worker loaded 1.5 ml of saline or nitroglycerine solution in a 5-ml syringe (taped to prevent recognition on the basis of colour) and instilled it intranasally with an opaque intravenous cannula (Angiocath).

Anaesthesia was induced 30 seconds after the administration of the solution, with a sleep dose of sodium thiopentone 4–6 mg/kg followed by suxamethonium 1.5 mg/kg. The induction drugs were administered within 40–50 seconds. Laryngoscopy and tracheal intubation were performed after the onset of apnoea; this took not more than 30 seconds. A patient was withdrawn from the study when difficulties in intubation occurred or if intubation was not accomplished at the first attempt. Following tracheal intubation, the lungs were ventilated with 33% oxygen in nitrous oxide, delivered through a Bain system with a fresh gas flow rate of 100 ml/kg.[4] Systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and heart rate (HR) were recorded during laryngoscopy (time zero) and then at intervals of 1, 3, 5 and 10 minutes thereafter. Surgical stimulus, analgesic supplements or inhalational anaesthetics were avoided during the period of study. Mean arterial pressure was calculated using the formula MAP = 1/3 (SAP + 2DAP).

Student's *t*-test for paired observations was used for analysis within groups, and for unpaired observations for analysis between groups.

Results

The pre-induction patient data were comparable in both groups (Table 1).

Heart rate. Changes in heart rate were insignificant when compared with pre-operative values in both the groups throughout the period of investigation (Fig. 1).

Table 1. Pre-induction patient data for both groups.

	Group 1 (normal saline) (n = 20)	Group 2 (nitroglycerine) (n = 20)
Mean (SEM) age, years	48.3 (2.9)	47.9 (2.7)
Range	40–55	40–58
Sex, M:F	12:8	10:10
Mean (SEM) weight, kg	70.8 (4.7)	73.2 (3.6)
Range	45–90	52–85
Mean (SEM) HR, beats/minute	72.1 (2.6)	76.6 (3.4)
Mean (SEM) SAP, mmHg	137.7 (3.4)	136.0 (3.2)
Mean (SEM) MAP, mmHg	103.9 (2.5)	103.2 (2.4)
Mean (SEM) DAP, mmHg	87.0 (2.2)	86.8 (1.9)

Blood pressure. A significant increase in SAP as well as MAP was seen in the control group at 0, 1 and 3 minutes. On the other hand, SAP and MAP in the nitroglycerine group were significantly lower than the control values at 1, 3 and 5 minutes. The value returned to basal levels within 10 minutes in all the patients and none of the patients had a decrease in SAP of more than 20 mmHg. Between-group analysis revealed significant differences between the changes in MAP and SAP during the first 5 minutes of investigation (Fig. 1).

ECG. No evidence of ischaemia was seen in any of the patients of either group.

Discussion

Our results demonstrate that the intranasal administration of nitroglycerine solution, 30 seconds before a thiopentone, suxamethonium induction sequence, attenuates the pressor response to direct laryngoscopy and tracheal intubation in treated hypertensive patients.

Fassoulaki and Kaniaris[3] demonstrated similar results in normotensive patients. They attenuated the pressor response to tracheal intubation using 60 mg of nitroglycerine solution instilled intranasally one minute before induction. We have previously achieved similar results with a much lower dose (0.75 mg) in normotensive patients (unpublished observations). In this study we again used 0.75 mg nitroglycerine, which is 80 times less than the dose used by previous workers. Hill *et al.*[5] showed that the intranasal administration of 0.8 mg nitroglycerine solution achieves peak plasma levels in 1–2 minutes and that these levels are sufficient to produce clinical effects of the drug. The dose of nitroglycerine used by us was similar to that used by Hill *et al.*[5] and, therefore, we expect peak plasma levels and the clinical effects of the drug to occur within 1–2 minutes after its nasal instillation. The design of the present study allows for the performance of laryngoscopy and intubation when the plasma levels of nitroglycerine should be at their peak.

A number of other drugs have been used to suppress the circulatory responses to laryngoscopy and tracheal intubation in normotensive patients. They include topical[6] and systemic[7] lignocaine, both of which only partly suppress the response. Alpha-blockers,[8] sodium nitroprusside[9] and hydrallazine[10] have also been used. The use of sodium nitroprusside usually necessitates invasive monitoring, which may not always be justified. Midazolam[11] and deep inhalational techniques[12] have also been recommended but the response is variable. Fentanyl (6 μg/kg) abolishes circulatory responses to tracheal intubation but may cause postoperative respiratory depression if the duration of anaesthesia is brief.[13]

Complications of the pressor response that follows laryngoscopy include myocardial ischaemia,[2,14] cardiac

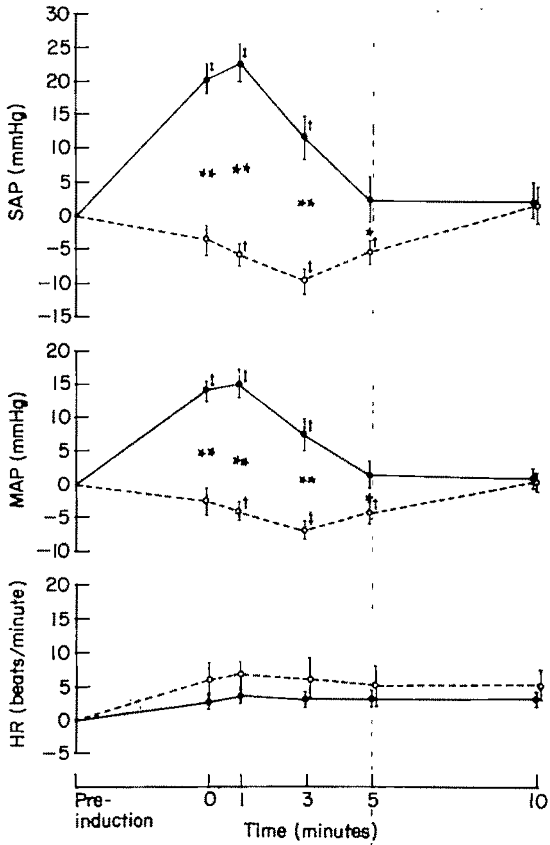

Fig. 1. Comparison of haemodynamic changes from control values of SAP, MAP and HR. Mean (SEM). Significant differences between groups: * $p < 0.05$, ** $p < 0.001$. Significant changes from control value, within each group: † $p < 0.001$, ‡ $p < 0.001$. ●, Control; ○, nitroglycerine.

failure,[15] intracranial haemorrhage[15] and increases in intracranial pressure.[16] Studies of hypertensive patients have shown that the pressor response to laryngoscopy is exaggerated in these patients and that it is associated with a marked increase in the noradrenaline levels in the blood.[17] Surgical patients with hypertension have also been shown to carry an increased risk of peri-operative complications.[18] Prys-Roberts and colleagues[19] found that the tachycardia and pressor response may be partly obtunded by the use of beta-adrenergic antagonists. Recently, intravenous metoprolol has been shown to be effective in the prevention of these reflex cardiovascular responses to laryngoscopy and intubation.[20] However, the intravenous administration of beta-blockers has long-lasting effects that may not be desirable.

Intranasal nitroglycerine is rapidly absorbed, short-acting, safe and economical.[5] It may be a convenient alternative to the agents mentioned above. Another advantage of this drug is its action on coronary haemodynamics, which causes an increased myocardial blood flow and improved myocardial oxygen balance.[21] Reflex tachycardia may, however, accompany the use of nitroglycerine and this can offset the beneficial effects on myocardial oxygen balance. Previous workers have reported persistent tachycardia after the use of intranasal nitroglycerine,[3] which could have been because of the higher doses used by them. Heart rate did not change significantly in either of the groups in our study. This may be because all of our patients were receiving beta-blockers for hypertension. Thus we cannot extrapolate our data to hypertensive patients treated with drugs other than beta-blockers. However, we do believe that intranasal nitroglycerine in a dose of 0.75 mg is safe, since Hill *et al.*[5] also did not report tachycardia in their cases who received intranasal nitroglycerine in a dose similar to that used by us.

In conclusion, we suggest that intranasal nitroglycerine, in a dose of 0.75 mg, is a safe, rapid and convenient method of attenuating the pressor response to laryngoscopy and tracheal intubation in treated hypertensive patients.

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A comparison of halothane and trichloroethylene with isoflurane. A study of drawover air anaesthesia with the Triservice anaesthetic apparatus

S. Q. M. Tighe, MBBS, FFARCS, Senior Registrar, Royal Naval Hospital Haslar, Gosport, Hampshire PO12 2AA, R. J. Pethybridge, BSc, PhD, Principal Statistician, The Institute of Naval Medicine, Alverstoke, Gosport, Hampshire PO12 2DP.

Summary

Induction and recovery times were not significantly different between two groups that received halothane with trichloroethylene and isoflurane, respectively. Maintenance of anaesthesia and analgesia was also satisfactory. Isoflurane resulted in a higher heart rate ($p < 0.01$), a lower respiratory rate ($p < 0.01$) and a higher inspired oxygen concentration ($p < 0.05$). Respiration may be more efficient. Other potential advantages of isoflurane for anaesthesia in the field are discussed. Despite the fact that it is 15 times more expensive, the use of isoflurane as sole agent is recommended.

Key words

Anaesthetic techniques; inhalational.
Anaesthetics, volatile; halothane, isoflurane, trichloroethylene.

The use of the Triservice anaesthetic apparatus (TSA)[1] with halothane, trichloroethylene (Hal/Tce) and oxygen-enriched air has proved satisfactory in military anaesthesia[2-4] and could have advantages in other difficult environments.[5] It may also have a place in general hospital practice because of the increasing interest in anaesthesia without nitrous oxide.

The Oxford Miniature Vaporizer (OMV) is supplied with interchangeable scales to be used with a variety of anaesthetic agents. There have been no reports of the use of the TSA with agents other than halothane and trichloroethylene and only one of these was a controlled study.[2]

The use of Hal/Tce in a single OMV has been evaluated[6] but this method has drawbacks.[7] Isoflurane has properties which may make it a suitable sole agent for drawover anaesthesia, particularly for military use. This study was therefore designed to evaluate the standard technique and to compare it with the use of isoflurane under identical conditions.

Materials and methods

Approval was obtained from the hospital ethical committee. Forty-eight patients (servicemen), ASA grade 1, aged 18–40 years, who presented for minor orthopaedic and general surgery, gave their consent. They were randomly allocated to one of two groups.

Premedication was with papaveretum 0.3 mg/kg intramuscularly one hour pre-operatively. Prior to induction, four readings were taken of systolic, diastolic, mean blood pressure and pulse rate at 2.5-minute intervals, using a Datascope Accutorr 1 automatic blood pressure analyser. Induction of anaesthesia was effected with thiopentone 5 mg/kg, followed by suxamethonium 1 mg/kg to facilitate tracheal intubation. The lungs were then ventilated for six breaths using air enriched with 4 litres/minute of oxygen. After tracheal intubation, the subjects' lungs were ventilated with a tidal volume of approximately 10 ml/kg body weight, at 12 breaths/minute with either Hal/Tce (group A) or isoflurane (group B); the vaporizers were set at three-quarters of the full scale deflection. If spontaneous ventilation had not resumed after 3 minutes, the vaporizers were set to one-third of the scale and the ventilation reduced to 4 breaths/minute. A Hewlett-Packard Model 47210A end tidal carbon dioxide (P_{ECO_2}) monitor was attached after 6 minutes and ventilation continued to maintain a P_{ECO_2} of 6.5 kPa. The subject was excluded and investigated for atypical cholinesterase if spontaneous ventilation had not returned after 10 minutes.

The time taken from intubation to the onset of spontaneous ventilation was called the induction time. Inspired concentrations were subsequently adjusted according to clinical signs in order to maintain surgical anaesthesia. The oxygen flow was reduced to 1 litre/minute. The electrocardiogram, P_{ECO_2} and inspired oxygen concentration (F_{IO_2}) were continuously monitored, the latter with an Instrumentation Laboratory 404 polarographic oxygen meter.

The following recordings were made: the indicated concentration of volatile agent, F_{IO_2}, P_{ECO_2}, tidal volume, respiratory rate, minute volume; pulse rate and systolic, diastolic and mean blood pressures. All instruments were calibrated daily, except the Wright's respirometer used for the respiratory measurements. The halothane, trichloroethylene and isoflurane vaporizers were serviced before the study was commenced and were subjected to a calibration test at the conclusion. Their performance was found to be satisfactory. The start and end of surgery and anaesthesia were noted and the presence of any dysrhythmias, or signs of inadequate anaesthesia, recorded.

Oxygen was administered at 4 litres/minute at the conclusion of surgery and the patient's trachea extubated. The time from extubation to full orientation (name, rank, service number and date of birth) was noted. The quantity of anaesthetic agent used was also measured.

Details of the statistical methodology can be obtained from the authors (R.J.P.).

Results

Five patients were excluded from the trial because of protocol violations. There were 18 separate operative

Table 1. Patient data.

	Hal/Tce (group A) ($n = 22$)		Isoflurane (group B) ($n = 21$)	
	Mean	Range	Mean	Range
Age, years	26	17–37	27	17–38
Weight, kg	76	58–92	81	62–97

Table 2. Time indices.

	Hal/Tce (group A) ($n = 22$)		Isoflurane (group B) ($n = 21$)	
	Mean	Range	Mean	Range
Premedication–induction time, minutes	64	40–90	62	34–96
Induction time, minutes	6.8	3.8–9.4	6.2	3.1–10.0
Operative time, minutes	25	10–82	26	12–52
Anaesthetic time, minutes	40	20–102	42	24–67
Recovery time, minutes	16.4	8.5–32.5	18.2	9.0–34.8

procedures and there were no significant differences in the distribution of these between the two groups. A summary of patient characteristics is given in Table 1 and various time indices of anaesthesia and surgery, in Table 2. There were no statistically significant differences. The volumes, concentrations and costs of the anaesthetic agents delivered are summarised in Table 3.

Pre-operatively, four readings of blood pressure and heart rate were recorded over a 5-minute period in the anaesthetic room, followed by induction. The means of the first two (T_1) and the second two (T_2) readings were calculated. Recordings recommenced on transfer to the operating theatre. As a result, the time interval between induction and the start of recordings varied. It was considered necessary to compare measurements between subjects at the same intervals after induction. This approach also ensured that all patients were surgically stimulated. Data from the first 13 minutes were therefore excluded and means calculated for readings taken between periods 13–18 (T_3), 18–23 (T_4) and 23–28 (T_5) minutes after induction. A summary of averaged data values at times T_1–T_5 for the two groups is shown in Tables 4 and 5. Differences are discussed below.

Table 3. Average volumes, concentrations and costs of anaesthetic agents delivered.

	Mean	Range
Halothane		
Volume, ml	15	8–33
Rate, ml/minute	0.38	0.2–0.58
%(maintenance)	1.3	0.92–1.94
Cost, pence/hour	59	
Trichloroethylene		
Volume, ml	3.1	0.5–11.3
Rate, ml/minute	0.08	0.008–0.157
%(maintenance)	0.3	0.25–0.44
Cost, pence/hour	1.8	
Isoflurane		
Volume, ml	24	12–48
Rate, ml/minute	0.58	0.43–0.81
%(maintenance)	1.38	1.00–1.89
Cost, pence/hour	867	

Blood pressure. There were significant ($p < 0.01$) reductions in systolic, diastolic and mean blood pressures between the pre-operative and operative periods for both groups, but no significant differences between groups.

Heart rate. The Hal/Tce groups showed a slight reduction in heart rate, whilst the isoflurane group demonstrated a significantly higher pulse during the operative phase ($p < 0.01$).

Respiratory rate. The respiratory rates of the isoflurane patients were significantly ($p < 0.01$) lower than those in the Hal/Tce group. In addition, the isoflurane patients showed significant ($p < 0.05$) changes in rates across the time intervals.

P_{ECO_2}. There were no differences in mean profiles between the two groups.

Table 4. Average cardiovascular indices.

	Group	T_1*	T_2	T_3†	T_4	T_5
Systolic BP, mmHg	A‡	125	124	111	113	111
	B	121	118	107	107	106
Diastolic BP, mmHg	A	78	77	71	72	70
	B	75	73	66	67	65
Mean BP, mmHg	A	93	92	88	88	87
	B	91	91	82	82	79
Pulse rate, beats/minute	A	73	74	70	70	68
	B	68	70	80	82	78

* T_1 and T_2 correspond to the time intervals of the first and the last two pre-operative recordings, respectively.
† T_3, T_4 and T_5 correspond to the time intervals 13–18, 18–23 and 23–28 minutes after induction, respectively.
‡ A, halothane/trichloroethylene; B, isoflurane.

Table 5. Average respiratory indices.

	Group	T_3*	T_4	T_5
Respiratory rate, breaths/minute	A†	30.1	30.2	29.6
	B	21.5	25.5	24.6
P_{ECO_2}, kPa	A	6.57	6.60	6.69
	B	6.71	6.51	6.77
F_{IO_2}	A	0.362	0.356	0.359
	B	0.394	0.398	0.405
Tidal volume, litres	A	0.199	0.202	0.191
	B	0.232	0.220	0.211
Minute volume, litres/minute	A	5.83	6.02	5.55
	B	4.80	5.43	4.87

* T_3, T_4 and T_5 correspond to the time intervals 13–18, 18–23 and 23–28 minutes after induction, respectively.
† A, halothane/trichloroethylene; B, isoflurane.

F_{IO_2}. The isoflurane group demonstrated significantly ($p < 0.05$) higher F_{IO_2} values than the Hal/Tce group.

Tidal volume. There were numerically higher values for isoflurane patients (12.2%), but no significant difference between groups.

Minute volume. No significant differences were found between the two groups, although the values for the Hal/Tce subjects were numerically larger (13.1%).

From 12 patients in each group it was possible to study data recorded during anaesthesia but prior to surgery. Surgical stimulation resulted in a significant ($p < 0.05$) increase in minute volume in both groups: 0.84 and 1.15 litres/minute for Hal/Tce and isoflurane, respectively. With Hal/Tce, this was a result of an increase in respiratory rate ($p < 0.05$) and not tidal volume. F_{IO_2} decreased significantly ($p < 0.05$) in both groups, by 3.4% and 4.8%, respectively. There were no other significant changes.

Discussion

Study design. The study was designed to simulate field conditions as closely as is possible in the hospital environment. The patients were selected from a population of those at risk as military casualties. They were premedicated so as to simulate analgesia given in the field. A 30–90 minute premedication–induction interval was permitted to account for the variability of administration and absorption of analgesics seen in this environment.[4] Intubation was carried out with suxamethonium, as all casualties are assumed to be at risk of aspiration. In order to avoid hyper- or hypocapnia, excessive depth of anaesthesia, breath-holding and coughing during induction, the timing of changes in respiratory rate and vaporizer settings was rigidly adhered to, after the optimum had been established in a pilot trial.

Induction. It might be expected that induction with isoflurane would be faster than with Hal/Tce because of the lower blood/gas solubility of the former.[8] This was not confirmed and probably reflects the induction technique, as the subjects were ventilated for up to 10 minutes. This method is recommended; induction was smooth, quick and uncomplicated in both groups.

Maintenance of anaesthesia. Indicated concentrations of Hal/Tce (range 0.25–0.44% trichloroethylene, 0.92–1.94% halothane) did not differ greatly from those reported by Knight and Houghton[2] (0.5–0.75% trichloroethylene, 0.75–1.5% halothane). It was surprising that so little isoflurane was required (1.0–1.89%, mean 1.38%) when it is considered that the MAC value of isoflurane is 1.53 times that of halothane.[9]

Analgesia may have been less intense in the isoflurane group, as there was an insignificantly greater increase in minute volume on surgical stimulation and a higher pulse rate during maintenance. However, a higher heart rate is to be expected in this young population[9] and the respiratory rate was subsequently lower than in the Hal/Tce group.

The use of the analgesic properties of isoflurane during general anaesthesia has not been previously reported, although it has been shown to be effective during labour in subanaesthetic concentrations.[10]

Cardiovascular effects. As previously reported, the pulse rates in the isoflurane group were significantly higher[9] but there was no difference in the blood pressure decrease.

In the young, fit population, the overall cardiovascular effect of isoflurane would appear to be more beneficial than that of halothane.[11] Even in the presence of hypovolaemia and inadequate intravenous resuscitation, as may occur with casualties of war, work in animals suggests that the effects of isoflurane are no more disadvantageous than those of other agents,[12] and may be less so.[13] It has been suggested that in hypovolaemia, the haemodynamic response may be more appropriate.[11]

There were no dysrhythmias with isoflurane, as opposed to three patients with nodal rhythm and two with ventricular ectopics in the Hal/Tce group. This confirms previous comparisons and is an advantage in the field.

Respiratory effects. The significant reduction in respiratory rate seen in the isoflurane group, has been previously reported in a comparison with halothane.[14] Trichloroethylene is associated with tachypnoea and can therefore be expected to exacerbate any difference between isoflurane and halothane in this respect. The P_{ECO_2} was the same but, although statistically insignificant, the tidal volume was higher (by a mean of 12.2%) and the minute volume lower (by a mean of 13.1%) in the isoflurane group. This suggests that respiration is more efficient with isoflurane, possibly as a result of the improved ratio of deadspace to tidal volume that accompanies a reduction in respiratory rate. This assumption is supported by the significant increase in F_{IO_2}, as this is inversely proportional to minute volume. Oxygen is in short supply in the field. The use of isoflurane would allow lower flow rates of additional oxygen and thus conserve stocks.

Recovery. Previous comparisons of the speed of recovery from halothane and isoflurane anaesthesia have shown little or no difference,[15] faster recovery[16] and slower recovery.[17] In this study it was expected that recovery with isoflurane would have been quicker than with Hal/Tce, mainly as a result of the absence of trichloroethylene and its sedative metabolites.[18] However, there was no significant difference; recovery in the isoflurane group was prolonged, with a mean of 18.2 minutes compared with 16.4 minutes. This was particularly surprising when it is considered that maintenance concentrations were much lower than those expected. The recovery times for Hal/Tce were much longer than those previously reported (5 minutes)[2,4]

but these studies included patients that had been paralysed and ventilated with low concentrations and the endpoints differed.

Recovery from isoflurane anaesthesia has been reported to be complicated by delirium.[19] There was no difference in this respect between the two groups in this study. The only noticeable problems were excessive salivation and occasional laryngeal stridor, attributed to the lack of antisialogogue premedication.

Cost and quantities. There was a difference of 7.4 ml/hour in the total volumes consumed. The use of isoflurane would be 15 times more expensive than Hal/Tce (867p versus 61p/hour). This would be slightly offset by the requirement for only one OMV, the most expensive component of the TSA.

Other considerations. Unlike halothane, isoflurane is resistant to biotransformation and is not contraindicated for the second anaesthetic invariably required by military casualties for secondary suturing.[3] It is more appropriate for anaesthesia in the presence of head injury[20] and the physical properties of isoflurane are suitable for field use.[8]

Conclusions

A technique for use of the TSA with halothane and trichoroethylene is described. Comparison with isoflurane as a sole agent showed this to provide similar conditions of anaesthesia and analgesia, with the added advantages of a lower respiratory rate, more economical use of oxygen and the requirement for only one vaporizer. Respiration may be more efficient. Isoflurane has other theoretical advantages which make it suitable for military anaesthesia. It is recommended for this purpose, provided that hypovolaemia is adequately corrected. Cost may preclude the use of isoflurane elsewhere.

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Correspondence

Cardiac output during an anaphylactoid reaction

Cardiac output has only rarely been measured during an anaphylactoid reaction in man because of the nature of the condition. We report here its measurement using oesophageal Doppler ultrasound.

A 15-year-old boy who weighed 65 kg presented for craniotomy to excise a large cystic lesion in the parietal region. He had been otherwise healthy apart from recent onset of epilepsy. He had undergone an uneventful anaesthetic for dental surgery as a young child and gave no history of atopy or previous drug reactions though, on questioning his mother after the event, it was discovered that he had suffered intermittently from eczema throughout his childhood. His drug therapy consisted of phenytoin 100 mg tds, carbamazepine 200 mg bd and dexamethasone 4 mg qid orally.

Premedication was with diazepam 10 mg orally given about one hour before induction of anaesthesia, which was with intravenous infusions of alfentanil (40 mg/hour for 5 minutes then 4 mg/hour) and methohexitone (100 mg bolus then 500 mg/hour). Neuromuscular blockade was obtained with a bolus of alcuronium 20 mg intravenously. The lungs were ventilated with 100% oxygen throughout the procedure. A tracheal tube was inserted and a Doppler ultrasound probe passed into the oesophagus. The patient was normotensive and the lungs were easily ventilated during the induction period.

The lungs became difficult to ventilate about 10 minutes after induction and a widespread urticarial rash developed. Widespread rhonchi were heard on auscultation of the chest. The infusions were stopped and anaesthesia maintained with halothane 0.5%. An intravenous bolus of chlorpheniramine 10 mg was given. The blood was found to be frankly cyanotic

All correspondence should be addressed to Dr J. N. Lunn, Editor of *Anaesthesia*, Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, United Kingdom.

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on arterial cannulation, and hypotension developed. Aminophylline 250 mg and hydrocortisone 100 mg were given intravenously and an infusion of salbutamol 0.5 mg/hour commenced. Plasma protein solution (800 ml) and Ringer's lactate solution (1000 ml) were rapidly infused.

An Accucom monitor was connected to the ultrasound probe approximately 30 minutes following induction and calibrated using a suprasternal ultrasound probe. At this time systemic blood pressure was 92/53 mmHg, heart rate 92 beats/minute and the cardiac output was measured as 10 litres/minute. The patient's condition resolved over the next 2.5 hours and the cardiac output gradually decreased to 6.2 litres/minute.

Blood samples were taken during this period and for 24 hours, which were later analysed by Dr J. Watkins at the Supraregional Protein Reference Unit in Sheffield. These showed no evidence of complement or immunoglobulin involvement. The patient subsequently underwent an uneventful anaesthetic with different agents for excision of a pilocystic astrocytoma.

This patient developed an anaphylactoid reaction to one of the anaesthetic agents used and, by chance, we had the ability to measure the patient's cardiac output using an Accucom cardiac output monitor. This is the first report of measurement of cardiac output during an anaphylactoid reaction using this technique, as far as we are aware. On review of the literature, only two previous reports of measurements during reactions to anaesthetic agents were found and these used different techniques. In one, measurement of cardiac output was made using dye dilution [1] and the other used two-dimensional transoesophageal echocardiography; [2] both reports showed an increase in cardiac output. The absolute accuracy of the Accucom measurements is questionable because estimated values for the patient's weight were entered into the monitor to enable it to calculate the cross-sectional area of the aorta. However, the monitor has previously correlated well with other methods of measuring cardiac output [3] and it is reasonable to assume that the patient's output was abnormally high when first measured and gradually decreased to near normal levels over the next 2.5 hours.

It is possible that the drugs administered in treatment of the reaction resulted in an increased cardiac output, since some have a positive inotropic effect. It is more likely that it was due to histamine release either indirectly, by increased sympatho-adrenergic activity, or as a result of a direct effect on the myocardium.[4]

Conventionally, adrenaline is advocated for treatment of cardiovascular collapse as a result of anaphylactoid reaction [5] but our findings suggest that if hypotension is unresolved by rapid intravenous infusion of plasma, administration of a pure alpha-adrenergic agonist like methoxamine might be more logical. The administration of adrenaline in the presence of hypoxia, as in this case, may also precipitate ventricular fibrillation.

Division of Neuroanaesthesia,
Institute of Neurological Sciences,
Southern General Hospital,
Glasgow G511 4TF

R.P. Alston
P.D. Oates

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Bowel sounds

Drs Shelly and Church (*Anaesthesia* 1987; **42:** 207–9) have highlighted a very important clinical observation that deserves wider dissemination.

When nutritional support is considered for the patient whose lungs are ventilated artifically, one of the first questions that seems to be asked is 'Are bowel sounds present?'. Their reported absence results in either postponement of nutritional support or the prescription of total parenteral nutrition inappropriately.

Our recent experience shows that approximately 55% of patients referred to the clinical nutrition team from the intensive therapy unit (ITU) at the Central Middlesex Hospital for consideration of nutritional support, are fed enterally. The underlying pathological processes determine whether we initially prescribe enteral nutrition (EN) or total parenteral nutrition (TPN) but, generally, TPN is prescribed after extensive abdominal surgery or in the presence of abdominal sepsis. The presence or absence of bowel sounds rarely alters our decision, which is established using other clinical criteria. In particular, EN would be contra-indicated in the presence of gross abdominal distension or significant volumes (greater than 400 ml in 24 hours) of gastric aspirate. EN is therefore our first-line treatment for most ITU patients. Full strength feed is

administered as a continuous infusion. This does not, as is often thought, cause diarrhoea, which is generally related to antibiotic treatment.[1]

We prefer to feed via a fine-bore long nasoduodeno-jejunal tube since gastric emptying does seem to be adversely affected in the critically ill. In our hands approximately 50% of 110 cm polyurethane naso-enteral tubes (Corpak, Wheeling, IL, USA) have passed spontaneously into the duodenum after 24 hours (unpublished observations). Those that have not, can be manipulated under fluoroscopy. We prefer the nasoduodenal or jejunal route since this minimises the risk of regurgitation and aspiration of feed[2] in the presence of gastroparesis or atony.

Undoubtedly, enteral nutrition is the preferred form of nutritional support in the presence of a functioning gastrointestinal tract[3] (whether by naso-enteral tube, gastrostomy, duodenostomy or jejunostomy), since it has fewer potential technical and metabolic complications than TPN. EN has an added advantage over TPN in that it is approximately one-eighth of the cost. Our policy is therefore to apply the most simple and clinically effective method of support for each patient and we find that early enteral nutrition is appropriate for a large number of ITU patients, including those whose lungs are ventilated. We agree that the presence or absence of bowel sounds should be abandoned as an indicator of suitability for enteral feeding and, therefore, strongly support the suggestions of Drs Shelly and Church.

Central Middlesex Hospital,
London NW10 7NS

J.J. Payne-James
R.G. Rees
D.B.A. Silk

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The anaesthetist and Maternity Services Liaison Committees

An article on the role and structure of the Maternity Services Liaison Committee (MSLC) by Jo Garcia in *Health Trends* gives the result of a national survey of policy and practice in midwifery in English Health Districts.[1] The existence and structure of an MSLC was one of the topics covered. Of the 161 respondents in Districts with planned or existing MSLCs, 130 gave information about the Committee's composition. Nearly all the Committees had a common core of professional members that consisted of one or more consultant obstetricians, consultant paediatricians, midwives, general practitioners and administrators. Many included District Medical Officers or other community physicians, health visitors, social workers and health education officers. Fifty-six percent had one or more lay members. Some respondents mentioned that appropriate professionals might be asked to join the Committee for particular items of business but anaesthetists were not mentioned.

As Consultant Anaesthetist Member of the Wales Perinatal Mortality Initiative Survey Group[2] I visited 20 units in nine District Health Authorities in Wales and found that 12 units did not have an anaesthetist who was a member of a MSLC. In two other units the anaesthetist member of the MSLC was not the most actively involved in the obstetric unit and there was lack of feedback to the obstetric anaesthetist.

MSLCs are Committees at Health District level which were formed on the recommendation of the Maternity Services Advisory Committee.[3] One of the functions of the MSLCs is to agree on procedures for good communication between sectors of the service and to report regularly to their District Health Authorities. They are expected to play a key role in future provision of good maternity care.

Since these are important Committees with input into District Health Authorities, should we not ensure that there is an obstetric anaesthetist as a member of these bodies so that we can influence the provision of maternity care and also provide a feedback to all anaesthetists involved in maternity units in the District?

Glan Clwyd Hospital,
Bodelwyddan,
Rhyl, Clwyd

B. Owen

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Nitrous oxide and oxyhaemoglobin dissociation

Drs Shah, Anderson and Bergman reported that nitrous oxide produced a small, statistically insignificant shift to the right of the oxyhaemoglobin dissociation curve (*Anaesthesia* 1986; **41:** 586–8), in contrast to the 9 mmHg left shift reported by Fournier and Major.[1] We have reported findings very similar to those of Dr Shah

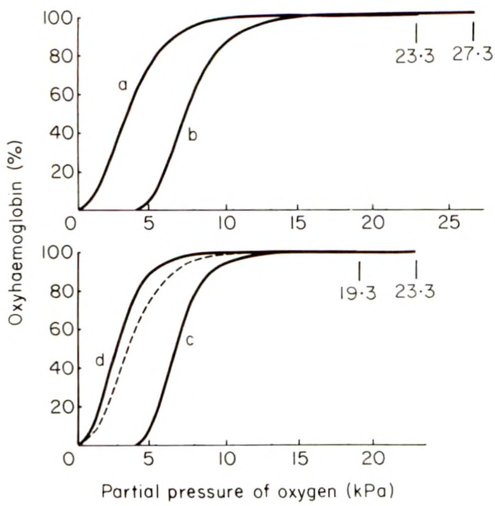

Fig. 1. Measurements of the oxyhaemoglobin dissociation curve of normal blood samples between 0 and 23.3 kPa oxygen at 37°C. *Curve a.* The curve as normally measured without nitrous oxide using oxygen electrode calibration points 0 and 23.3 pKa. *Curve b.* The curve measured in the presence of nitrous oxide using oxygen electrode calibration points of 4 and 27.3 kPa. Due to the limited size of the chart paper bed, this curve had to be drawn on photoreduced paper after appropriate recalibration of the machine and then enlarged for plotting with curve a. *Curve c.* The curve measured in the presence of nitrous oxide but with the oxygen electrode calibrated to points 4 and 23.3 kPa, i.e. the zero offset has been accepted but the original manufacturer's instructions regarding the setting of the upper point on the top right-hand corner of the graph paper have been followed. *Curve d.* Curve c replotted so that zero oxygen pressure corresponds to zero on the chart paper, so that it may be compared directly to a normal curve. An apparent left shift of 6 mmHg is produced at P_{50} when compared with a normal curve, shown in the lower panel by a dashed line.

and colleagues, i.e. small, statistically insignificant right shifts. In our study nitrous oxide produced a 1.5 mmHg mean right shift in the blood of 10 volunteers and a 1 mmHg mean right shift in the blood of 10 patients who underwent nitrous oxide : oxygen : pethidine anaesthesia.[2] A 0.21 kPa right shift in the presence of nitrous oxide was also recently reported by others[3] who used intrumentation different from that used by Shah, by Fournier and by ourselves. We were intrigued by the results of Fournier and Major since we had conducted our study quite independently using an almost identical protocol and the same instrumentation. After careful perusal of the publication by Fournier and Major, we concluded that their results may have been due to a calibration error of the Hem-O-Scan machine produced by compression of the *x*-axis scale.

We found, like Fournier and Major, that the oxygen electrode was 'offset' in the presence of nitrous oxide. This offset was less than 10 mmHg with one of our electrodes and we were able to bring the zero and high (175 mmHg) calibration points back to the actual points on the graph paper by electronic adjustment of the machine in the usual manner. However, with another of our electrodes, the offset was so great that, like Fournier and Major, we were unable to align the pen with the zero on the chart paper for the zero calibration of the oxygen electrode. Our offset was about 4.0 kPa; that of Fournier and Major was 5.3 kPa. Like Fournier and Major, we accepted this offset. *This in turn required that the high calibration point of the electrode also be offset to the right by the same amount on the x-axis of the chart paper* (curve b, Fig. 1). This is physically impossible with the Hem-O-Scan machine unless photoreduced paper is used. Failure to offset the high calibration point by the same amount as the zero calibration point, results in a compression of the scale of the *x*-axis (curve c, Fig. 1) and the resulting curve, when replotted so that the zero points coincide, is artefactually strongly shifted to the left (curve d, Fig. 1).

No mention was made of this problem or of photoreducing the chart paper in the detailed methods section of the publication by Fournier and Major, so we suggest the possibility that their results may have been due to this calibration error.

Further studies seem to be indicated since different electrodes seem to be affected to different extents by nitrous oxide. This is, of course, of no relevance if appropriate calibration procedures are carried out before any measurements are made, and cannot *per se* explain the results of Fournier *et al.* Most manufacturers of polarographic electrodes appear to have overcome this problem[4] but it is a potential source of error of which users of these electrodes should be aware.

Departments of Anaesthesia and Intensive Care and Haematology, Flinders Medical Centre, Bedford Park, Australia 5042

W.B. RUNICMAN
A.H. ILSLEY
R.J. CARAPETIS
D.G. SELBY
R.G. RYALL

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Shaping tracheal tubes

It is difficult to intubate the trachea when the vocal cords cannot be exposed, even more so if the tip of the epiglottis is barely visible. Under these circumstances a stylet is commonly employed to improve the curvature of the tracheal tube. Other stratagems include intubation with topical anaesthesia with the patient awake, use of a tracheal tube with lesser diameter or of an alternative kind of laryngoscope blade, blind nasal intubation with the patient awake or anaesthetised, a retrograde method via the classical cricothyroidotomy, fibreoptic laryngoscopy, use of a gum elastic catheter or bougie and combinations of these measures.[1,2]

Many years ago, having witnessed breakage of a metal stylet and aspiration of its tip by the patient, we abandoned the use of stylets in favour of the technique described below.

When a difficult intubation is anticipated or experienced, the tip of a polyvinyl tracheal tube (3–3.5 cm) is bent acutely into a golf club shape and that shape maintained during immersion in iced water, until fixed (2–3 minutes) (Fig. 1, A1). The remainder of the curvature of the tube may likewise be altered to permit easier insertion into the pharynx (Fig. 1, B).

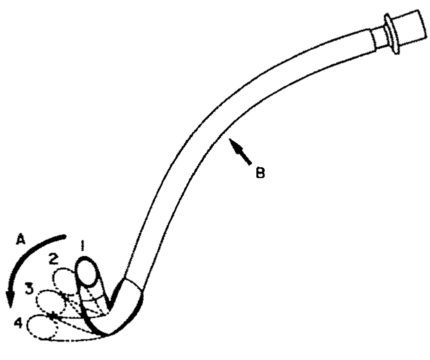

Fig. 1. Configuration of tracheal tube.

In practice, when the tip of the epiglottis comes into view on laryngoscopy, the epiglottis is lifted with the tip of the tracheal tube which is then slid along the interior surface until the glottis is passed. During this manouevre an assistant maintains gentle backward pressure on the cricoid cartilage to prevent oesophageal intubation. The tip gradually softens as the tube is advanced and the angle becomes less acute, and more easily enters the trachea (Fig. 1, A4). The assistant confirms its passage by tactile sensation. Insufflation of oxygen can be carried out as intubation progresses.

A stylet cannot be employed with this method since it might not easily be removed. The retrograde approach is not necessary and use of an expensive fibreoptic laryngoscope is avoided. We have not encountered any serious complications over a 20-year period.

Osaka Kohseinenkin Hospital,
4-2-78 Fukushima,
Fukushima-Ku,
Osaka, Japan

Y. KUBOTA
Y. TOYODA
H. KUBOTA
Y. UEDA

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Pleural aspiration with a central venous catheter

The report by C.M.S. Cooper (*Anaesthesia* 1986; **42**: 217) on pleural effusion drainage using a central venous catheter with FloSwitch, was interesting and brought to mind an occasion when a catheter was used to drain a pleural effusion, except that in this case, unfortunately, it was instrumental in producing the effusion in the first place.

A frail 88-year-old woman was anaesthetised for gastro-enterostomy. She was known to have a long history of chronic obstructive airways disease with two episodes in the preceding weeks of acute respiratory embarrassment which settled with bronchodilator therapy. A central venous catheter (Vygon Surcath 172.17) was placed in the right internal jugular vein after induction and blood was freely aspirated again after the patient was positioned on the operating table. The line was used to monitor central venous pressure (highest reading +3 cm H_2O) and for infusion of human plasma protein during the course of the procedure. The anaesthetic was uneventful and the patient was transferred to the recovery area after extubation. Shortly after, the patient vomited faeculent material and was initially thought not to have aspirated. However, respiratory distress was noted during the course of the next 10 minutes and the intensive care unit personnel were contacted.

The patient had rapid, shallow grunting breathing and was transferred immediately into the adjacent intensive therapy unit, pre-oxygenated with 100% oxygen, given 2.5 mg Diazemuls, her trachea re-intubated and intermittent positive pressure ventilation of the lungs restarted. Clear secretions were aspirated from the trachea. Chest X ray showed a right-sided pleural effusion and an attempt to obtain a blood sample from

the central venous catheter produced a watery sample.

The patient was placed in a head-down position and fluid drained freely and continuously during both cycles of ventilation. However, it was found that a much better flow rate was obtained if the central venous catheter was connected through a drip set to an underwater seal drain. The flow chamber of the drip set was removed with sterile scissors and connexion achieved with a Sims connector. A total of 2.3 litres of fluid was drained, with total resolution of the chest X ray changes. Spontaneous ventilation was re-established a couple of hours after admission to the intensive care unit and the patient was extubated and made a satisfactory recovery.

This shows that what goes in, may also come back out. This method of drainage avoided further trauma to a very frail old lady.

Anaesthetic Department, J.M. THORP
Monklands District General Hospital,
Airdrie ML6 0JS

Vomiting following ophthalmic anaesthesia

In their article about the effects on intra-ocular pressure of fentanyl and alfentanil in patients whose lungs were ventilated with halothane during ophthalmic operations (*Anaesthesia* 1986; **41:** 493–8) Drs Mostafa *et al.* assert that none of their patients vomited postoperatively. However, they state that their study period ceased intra-operatively 15 minutes after injection of the fentanyl/alfentanil, and no mention is made of a postoperative patient or ward visit. May I enquire, with respect, how the absence of postoperative emesis was therefore determined?

Studies[1] using similar anaesthetic and antiemetic agents in similar ophthalmic patients have shown vomiting rates of 5–38% within the first 24-hour postoperative period. Whether the addition of fentanyl/alfentanil and droperidol to nitrous oxide and halothane anaesthesia (as described by Dr Mostafa and his colleagues) renders this technique peculiarly anti-emetic, as their article leads one to believe, or whether emesis was not specifically enquired into, as appears to be the case, needs clarification.

Riyadh Armed Forces Hospital, A.A. VAN DEN BERG
P.O. Box 7897,
Riyadh 11159,
Kingdom of Saudi Arabia

Reference

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A reply

Thank you for giving us the opportunity to reply to Dr van den Berg's letter. We were not aware that we made assertions in our article (*Anaesthesia* 1986; **41:** 493–8) about the absence of vomiting in our group of patients. We merely noted an observation in one and a half sentences in the text!

Our study was concerned mainly with the immediate changes in intra-ocular pressure, heart rate and blood pressure following the administration of fentanyl or alfentanil. Our observation of these variables, therefore, lasted for 15 minutes following the injection of the trial drugs. The quality of our patients' recovery from anaesthesia in the *immediate* postoperative period was also noted. This included the incidence of postoperative vomiting. Patients were kept in the recovery room for 2 hours. During this time none had vomited. Patients were also routinely prescribed prochlorperazine 6.25–12.5 mg intramuscularly 6-hourly prn as a postoperative antiemetic. We visited our patients later on the ward but no note of vomiting was made; at the same time, no complaints were made spontaneously by either patients or nurses.

We agree with Dr van den Berg that the incidence of postoperative sickness is variable but we would be very alarmed if the incidence of the latter in our ophthalmic patients is as high as 38%. We have just concluded a clinical trial (unpublished) in which a similar anaesthetic technique and drugs were used, but we found that only 5% of the patients vomited postoperatively. Postoperative sickness may be produced by numerous factors. Anaesthetic technique and agents, site and type of operation and early, or liberal, administration of oral fluids postoperatively are only some.[1] In view of the multitude of these causes, we choose our technique and drugs meticulously, maintain normocapnia, administer droperidol 5 mg preoperatively and oxygen postoperatively. We also avoid inflation of the stomach with air prior to tracheal intubation, hypotension and overzealous suction of the oropharynx at the end of surgery. All these steps are necessary and should be effective in the reduction of the incidence of this hazard.[2] We also believe that droperidol has an important and integral part to play in our technique. Vomiting is not a common complication, owing to the great potency of this drug as an antiemetic agent. It has been shown that patients who received droperidol 1.25 mg did not vomit during the first 3 hours postoperatively.[3] Furthermore, in the same trial it was reported to be significantly more effective than saline, metoclopramide or domperidone in the reduction of both the occurrence and recurrence of postoperative nausea and vomiting.

Patients who undergo surgery under general anaesthesia may, despite all possible care, still vomit post-

operatively. We just have to consider that our small series of 50 patients were lucky not to suffer this miserable complication.

Royal Liverpool Hospital, S.M. MOSTAFA
Liverpool L7 8XP
Dudley Road Hospital, A. LOCKHART
Birmingham B18 7QH

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Prochlorperazine and vomiting after eye surgery

Completion of our study[1] (study 1) on 200 morphine with atropine premedicated ophthalmic surgical patients, which showed the antiemetic non-usefulness of intra-operative droperidol 0.035 mg/kg intravenously with induction, metoclopramide 0.14 mg/kg intravenously at the end of anaesthesia and prochloroperazine 0.18 mg/kg intramuscularly intra-operatively, coincided with the report of Fisher *et al.*[2] on the probable usefulness of a combination of antiemetics (promethazine and droperidol) in the reduction of postanaesthetic vomiting. Fisher's report received theoretical support by Howard[3] and both authors suggested that combinations of antiemetics may be more efficacious than the drugs used individually, as has long been recognised and used in the treatment of chemotherapeutic-induced vomiting.[4]

These publications prompted us to undertake two further studies (studies 2 and 3, involving 150 patients each, aged neonates to nonagenarians, undergoing all types of ophthalmic surgery) to evaluate the efficacy of various combinations of droperidol, metoclopramide and prochlorperazine, with saline control comparisons. Study 2 patients received oral diazepam with metoclopramide premedication (0.14 mg/kg of each) followed by a second antiemetic, either droperidol 0.035 mg/kg or prochlorperazine 0.0875 mg/kg intravenously with induction, or saline 1–2 ml as control. Study 3 patients received oral diazepam with droperidol premedication (0.07 mg/kg of each) followed by a second antiemetic, either metoclopramide 0.14 mg/kg or prochloroperazine 0.0875 mg/kg intravenously with induction or, again, saline as control.

Spontaneous or assisted ventilation with nitrous oxide, oxygen and halothane after an inhalational induction and tracheal intubation in children, or after intravenous induction and tracheal intubation using alcuronium pretreatment (0.03 mg/kg), thiopentone 3–4 mg/kg and suxamethonium 1.5 mg/kg in adults, was used in all patients. Appropriate pre-operative, operative and postoperative data (vomiting and analgesic requirements) were collected.

In study 1 the incidence of vomiting was 26% in the saline and droperidol groups, 28% after metoclopramide and 14% after prochlorperazine. In study 2 (a combination antiemetic study using pre-operative metoclopramide), the saline and droperidol groups both had incidences of vomiting of 20%, with an incidence of 14% in the prochlorperazine group. In study 3 (a combination antiemetic study using pre-operative droperidol), the controls had an incidence of vomiting of 36%, with 22% after metoclopramide and 16% after prochlorperazine.

Hence, surprisingly, no benefit was observed by combination of the antiemetics in the doses and routes described. However, though individually insignificant, the lower incidences of vomiting in the prochlorperazine groups in each study, when analysed collectively, yield an overall incidence of 15% in the 150 patients given prochlorperazine, a significantly lower rate ($p < 0.01$) than that seen in the other groups and overall. This favourable rate compares well with the incidences of 16% and 11% reported by Iwamoto[5] and Nikki[6] who used droperidol in comparable studies, and suggests that prochlorperazine 0.18 mg/kg intramuscularly intra-operatively or 0.0875 mg/kg intravenously with induction, is as efficacious as droperidol.

Further, the suggestions in study 1 that droperidol reduced the number of multiple vomiters and that prochlorperazine delayed the onset of vomiting, were not verified by studies 2 and 3. An interesting final observation in these three studies is that the overall higher incidence of vomiting expected in the 200 morphine premedicated patients (study 1) was, in fact, no higher than the overall rate seen in the 300 diazepam premedicated patients (studies 2 and 3); the rates were 24% and 21%, respectively.

Department of Anaesthetics, A.A. VAN DEN BERG
Riyadh Armed Forces Hospital,
P.O. Box 7897,
Riyadh 11159,
Kingdom of Saudi Arabia
Department of Community Medicine, A. LAMBOURNE
King Saud University,
P.O. Box 2925,
Riyadh 11472,
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Management of labour and delivery in a patient with Guillain–Barré syndrome

A clinical diagnosis of acute Guillain–Barré syndrome was made at 38 weeks' gestation in a 29-year-old woman who went into spontaneous labour 2 weeks later. Respiratory function was deemed adequate despite severe limb weakness.

After much consideration, an epidural was sited in the L_2–L_3 interspace; the initial dose of 4 ml 0.25% bupivacaine provided analgesia for 85 minutes. Subsequently, throughout labour, she received four top-ups of 4 ml 0.25% bupivacaine, each of which provided excellent analgesia for 85–110 minutes.

It was decided after 8 hours of labour to proceed to Caesarean section because of failure to progress allied to a persistent fetal bradycardia 65 minutes after the last top-up of 0.25% bupivacaine. The initial dose of 3 ml 0.5% bupivacaine gave a level of analgesia to T_{10}; a further 4 ml 0.5% provided satisfactory anaesthesia for the operation. A live female infant, Apgar scores 8 at 1 minute and 10 at 5 minutes, was delivered. Postoperative analgesia was maintained using an infusion of 0.25% bupivacaine at a rate of 3–5 ml/hour.

The patient's weakness increased at 20 days post partum despite initial improvement in symptoms and she was referred for plasmapheresis therapy. She did not require ventilatory support at any stage and at 3.5 months was able to walk with a frame.

Acute Guillain–Barré syndrome has been reported in pregnancy before, yet little information is available on the management of labour and delivery.[1] It was reported in one case that an epidural had been used in labour, but some months after complete recovery. The syndome has an incidence of 1.7 per 100000: 10–23% of patients require ventilation and there is a 7% mortality.[2]

We were aware of the possibility that exacerbation of the condition might be attributed to the epidural but it was considered that avoidance of any respiratory depressant drugs during labour and general anaesthesia for Caesarean section, was of utmost importance. It was of interest to note the very small doses of local anaesthetic required to provide excellent analgesia and that there were no apparent after effects attributed to the epidural.

York District Hospital,
Wiggington Road,
York YO3 8HE

E.M. MCGRADY

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Spinal anaesthesia for Caesarean section

It was interesting to read the letter from Drs Hollis, White and Procter (*Anaesthesia* 1987; **42:** 323) about the use of spinal anaesthesia for Caesarean section.

During the past two years in this maternity unit some 385 patients out of 1281 who required Caesarean section, received spinal anaesthesia; 0.5% plain bupivacaine was used in all cases. Interestingly, during the last 6 months, 45% of patients who required Caesarean section received spinal anaesthesia; this included emergency cases as well as elective cases, which testifies to the increasing popularity of the technique. It seems to me that this is due to the essential simplicity of the technique, the speed of onset, the intensity of anaesthesia and the rapidity of recovery. This last point, however, requires an awareness of, and willingness to administer postoperative analgesia rapidly in the recovery ward.

It is my practice to preload the patient with one litre of intravenous fluid, perform lumbar puncture in the left lateral position with a 25-gauge spinal needle and to inject 2.5 ml 0.5% plain bupivacaine over about 25 seconds. Less than 2.5 ml might, in my opinion, produce inadequate extent of block, except in patients of very short stature. This reliably produces a block that extends to T_{2-4}, which starts in 2 minutes and is complete within 5–10 minutes. The patient is kept on her left side until the obstetrician is ready to start, then turned supine with a lateral tilt. Ephedrine is given intravenously as required. No patient has had difficulty in breathing but a small number have commented on

tingling in the fingers which is short-lived.

It is exceptional for any complaint of discomfort to be made intra-operatively. This may be compared with some 10–15% of patients who experience pain or discomfort at various stages during epidural Caesarean section and may require supplementary analgesia and sedation. The patients are routinely followed up, with particular reference to any complaint of headache; if present, headache is actively managed with an epidural blood patch, which has given uniformly successful results. The incidence of headache is less than 6%, which is acceptable in view of the general satisfaction with this technique expressed by patients, obstetricians and midwives, as well as anaesthetists. Attention to detail in the technique must be meticulous to avoid inadvertent advance or retraction of the needle in the narrowed subarachnoid space of late pregnancy, and the rate of injection slow to avoid excessive spread. It is a technique easily mastered by registrars sufficiently experienced to undertake obstetric anaesthesia and is invaluable in emergency cases.

Plain 0.5% bupivacaine is, in my experience, a most useful and reliable agent for injection into the subarachnoid space and it should be used more widely for this purpose.

Royal Maternity Hospital,
Glasgow
I. Kirkwood

Betel nut chewing

This is with reference to the letter, To chew or not to chew, from Dr R. J. Cohen (*Anaesthesia* 1987; **42:** 220). In the Southeast Asian countries betel nut chewing is a very common, addictive practice; nut chewing is permissible even during religious fasts. In the adult population scheduled for anaesthesia, we thus make it a point to ask for possible nuts stacked away in the cheek, so to this we can add sweets and chewing gum!

T.N. Medical College and
B.Y.L. Nair Hospital,
Bombay 400 088, India
V.M. Divekar

Oximetry during transport

The recent review of pulse oximetry by Dr Taylor and Professor Whitwam (*Anaesthesia* 1986; **41:** 943–9) omitted to mention one situation in which we believe that the use of a pulse oximeter adds greatly to patient safety, namely, during the transport of critically ill patients. The transfer of patients to and between hospitals is a time when the patients are at great risk; the levels of monitoring and intervention available are often far below those of even the most poorly equipped hospital. Anaesthetists are often involved in the transfer of critically ill patients, particularly when patients are intubated and ventilated, and it is the anaesthetist's responsibility to ensure the patient is transferred as safely as possible.

We have recently used a Bird 4400 portable pulse oximeter in the Careflight Community Medical Rescue Helicopter which operates from this hospital. When ventilated patients are transported by helicopter or by road ambulance, the usual auditory and visual clues that the patient's lungs are inadequately ventilated may not be apparent until hypoxia has reached an advanced stage, possibly to the point of tissue damage. In this situation a pulse oximeter with audible alarm, connected if necessary to a loudspeaker or intercom system, may give early warning of impending disaster. Pulse oximetry offers for the foreseeable future the only truly transportable means of continuously monitoring the state of patient oxygenation.

Helicopters offer a practical means for rapid inter-hospital transfer of patients and primary transfer of severely injured trauma patients. The patients involved often have controlled ventilation but the supplies of oxygen a helicopter can carry are limited by considerations of space and weight. The use of a pulse oximeter allows efficient use of the available supply because an unnecessarily high inspired oxygen concentration is avoided.

We believe that, with due regard to ever-present financial constraints, a pulse oximeter should be used to monitor critically ill patients during transfer to and between hospitals.

Westmead Hospital,
Westmead,
New South Wales
2145, Australia
S.R. Finfer
K.J. Wishaw

Needlestick injury from indwelling steel needle

A patient was scheduled for a minor procedure. A 23-gauge butterfly needle (Abbott) was sited in the dorsum of the hand so that the needle tip lay over the wrist joint. Anaesthesia was induced intravenously and she was transferred into the operating room. The anaesthetist's assistant grasped the wrist, with his thumb overlying the needle tip, and palmarflexed it to position the patient's arm. The needle tip pierced the patient's skin and inflicted a painful puncture on the assistant. On inspection immediately afterwards, a small ery-

thematous mark was visible on the patient's hand. The needle was withdrawn and a pressure dressing applied. There were no sequelae to patient or assistant.

This complication has also happened to another patient; the risk is present whenever the needle is sited such that the tip lies above the wrist joint on the extensor surface, except in children when the grip strength necessary to lift the arm is less. There is a high incidence of extravasation with steel needles,[1,2] with possible sequelae of tissue damage[3] or unavailability at a crucial time,[4] but direct needlestick innoculation from patient to operating theatre staff must also be considered a hazard.

The Royal Free Hospital,
London NW3 2QG

S.M. KINSELLA

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Index of computer programs

031.1.12

Author D.I. Jones (Princess of Wales Hospital, Coity Road, Bridgend, South Wales).

Title Princess of Wales Anaesthetic Record System (POWARS)

Description This is a suite of programs which allows the recording of anaesthetic and operation details and the production of statistics based on these records. Information recorded and analysed includes patient data, personnel involved, dates and times, type of surgery/anaesthesia, drugs, circuits and equipment used, and incidents that occurred.

The system is used at present to assist audit, personnel management and analysis of junior staff experience. There is a purpose-designed anaesthetic record sheet.

Language MS DOS and compiled MS BASIC (Hewlett–Packard Series 100)

Computing facility Hewlett–Packard HP150 with a hard disc (or two floppies).

Details of programs to be included in this catalogue should be sent to Dr M.J. Harrison, Department of Anaesthesia, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB. They should be of relevance to anaesthesia or intensive care. Programs that involve the application of the basic sciences, or teaching, will also be accepted Further details of the programs can be obtained from the department or person directly involved.

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The collator of this section is Dr L. Kaufman, MD, FFARCS, Anaesthetic Office, The Rayne Institute, University College, University Street, London WC1E 6JJ. Dr Kaufman is prepared to provide on request, and at a modest charge, a new additional service to our readers. References from January 1984 have been entered on data base. The data are held on Dbase II, cpm 86 and on Dbase III, MsDos and are available on disc, together with a program providing search facilities. Enquiries direct to Dr Kaufman at the above address please.

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Treatment and medication

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Anaesthesia, 1987, Volume 42, page 924

Notices

The Magill Gold Medal of the Association of Anaesthetists

A gold medal is to be presented by the Association of Anaesthetists of Great Britain and Ireland at intervals to an individual (medical, scientific or industrial) who, in the opinion of the Council, deserves the highest commendation for innovation in anaesthesia. Various individuals have already demonstrated their wish that Sir Ivan be commemorated in some way and have donated sums of money to enable the Association to do so. These and any other monies received will be used to defray the costs of the medal.

Research in anaesthesia

The President of the Association of Anaesthetists of Great Britain and Ireland and several Professors of Anaesthetics in Universities of the United Kingdom met the Assistant Director of the Wellcome Trust to discuss support for anaesthetic areas of interest. The following statement was agreed.

Wellcome Trust

The Wellcome Trust is an independent charity with funds of about £35 million (in 1986) disbursed by the Trustees monthly on advice from the Director, Assistant Director and Advisory Committees. The important feature of the Trust is flexibility. When support is required for unusual situations it is advisable to make a preliminary enquiry of the Assistant Director who will offer guidance. The Trust puts special emphasis on support for an identified individual rather than a post. Certain subjects from time to time are highlighted for support. Of interest to anaesthetists at present is neuroscience. Applications from anaesthetists have been sparse. The Assistant Director, Dr P.A.J. Ball, has kindly offered to discuss projects before formal application and to offer guidance.

Research Training Fellowships

The Trust supports individuals judged of a high calibre who need further training, usually for 2 years, after they have acquired a primary diploma, in the case of anaesthetists the FFARCS. This will furnish an opportunity to acquire experience in relevant techniques and disciplines, possibly leading to a University degree. A project and appropriate host department are required. An interview is an important part of the decision process.

Support for Senior Clinical Research Fellows

The Trust supports a number of individuals of outstanding promise in research for 5 years to enable them to become fully established. Most Fellows have proceeded to Chairs in open competition. It is important to identify the individual in advance and plan an optimum scheme with the Wellcome Trust.

Anaesthesia, 1987, Volume 42, page 925

Hazard notice

Breathing System Fittings, EME and Mallinckrodt

A recent investigation of a fatal accident has revealed that there were a number of preventable factors.

The 15- and 22-mm conical fittings in a disposable breathing system supplied by EME do not meet the appropriate British Standard. The small tapered tubing connectors to the Y-piece manifold can be easily disconnected. The right-angle swivel connector (Mallinckrodt Laboratories Ltd) supplied in 1979 did not meet the appropriate British Standard. The breathing system had been re-sterilised and re-used. The pressure alarm was probably turned off during the incident.

All breathing system fittings must comply with the appropriate British Standard and *Health Equipment Information Bulletin 8(HEI)150* should be consulted. Any right-angled swivel connectors supplied by Mallinckrodt Laboratories before 1985 should be scrapped. Disposable breathing systems supplied by EME Ltd which incorporate a 15-mm patient Y-piece manifold and a 22-mm male connector should be withdrawn. Single use breathing systems must not be re-sterilised or re-used since they may become degraded or distorted. See *Safety Information Bulletins SIB 24(85)32* and *SIB 29(86)39*.

Erratum

Anaesthesia, 1987, Volume 42, pages 387–393

Vecuronium infusions in patients with renal failure in an ITU

C. L. SMITH, J. M. HUNTER AND R. S. JONES

The first sentence of the second paragraph of the Summary (p. 387), should read:

There was a marked variation in the dose of vecuronium administered (0.01–0.065 *mg/kg/hour*).

In the fourth paragraph of the Results section (p. 390), the final sentence should conclude:

. . . a lower infusion rate sufficed (0.015 mg/kg/hour).

THIS PAGE CONCERNS YOU IF YOU ARE
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........................19

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I (full name).. offer my name as a candidate
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Qualifications (with dates)..

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*See the reverse of this page for details of membership categories.
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Articles for *Anaesthesia* should be prepared in accordance with *Uniform requirements for manuscripts submitted to biomedical journals* (*British Medical Journal* 1979; **1:** 532–5) except that the titles of journals in the reference section should be given in full (see below). A reprint of these requirements of which this notice is a summary, can be obtained from the *British Medical Journal* price 50 pence (UK).

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The second page should carry a summary of not more than 150 words. The summary should state the purpose of the study or investigation, basic procedures, main findings and their statistical significance, and the principal conclusions.

Do not use abbreviations except for units of measurement (e.g. mg, cm, etc.).

Key (indexing) words. Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers. Use terms from the Medical Subject Headings list from *Index Medicus*. The Editor may modify these at proof stage to conform with agreed practice of certain other anaesthetic journals in the English language.

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The text of observational and experimental articles, case reports, etc. is usually divided into sections with the headings *Introduction, Methods, Results* and *Discussion*. Long articles will need subheadings within some sections to clarify their content.

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Headings: three steps of heading may be used in typescripts:

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Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by arabic numerals. References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration. Use double or treble spaced typing.

Use the form of reference adopted by the US National Library of Medicine and used in *Index Medicus*. Use the style of the examples cited at the end of this section.

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Examples of correct form of references

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JOURNAL

Standard journal article—(List all authors)

SOTER NA, WASSERMAN SI, AUSTEN KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *New England Journal of Medicine* 1976; **294:** 687–90.

Corporate author

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. *Scandinavian Journal of Clinical Laboratory Investigation* 1976; **36:** 119–25.

Anonymous. Epidemiology for primary health care. *International Journal of Epidemiology* 1976; **5:** 224–5.

BOOKS AND OTHER MONOGRAPHS

Personal author(s)

OSLER AG. *Complement: mechanisms and functions.* New York: Prentice-Hall, 1976.

Corporate authors

American Medical Association Department of Drugs. AMA drug evaluations, 3rd edn. New York: Publishing Sciences Group, 1977.

Editor, compiler, chairman as author

RHODES AJ, VAN ROOYEN CE, *comps. Textbook of virology: for students and practitioners of medicine and other health sciences*, 5th edn. Baltimore: The Williams & Wilkins Co., 1968.

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WEINSTEIN L, SWARTZ MN. Pathogenic properties of invading micro-organisms. In: SODEMAN WA Jr, SODEMAN WA, eds. *Pathologic physiology: mechanisms of disease.* Philadelphia: W.B. Saunders, 1974: 457–72.

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National Center for Health Statistics. Acute conditions: incidence and associated disability, United States, July 1968—June 1969. Rockville, MD: National Center for Health Statistics, 1972. (*Vital and health statistics, Series* **10:** Data from the National Health Survey, No. 69) [DHEW publication No. (HSM) 72–1036].

OTHER ARTICLES

Newspaper article

SHAFFER RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help to cure alcoholism and insomnia, explain mental illness. How the messengers work. *Wall Street Journal* 1977 Aug 12: 1(col 1), 10(col 1).

Magazine article

ROUECHE B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971 Sept 4: 66–81.

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Contents: Anaesthesia, vol. 42, no. 8, August 1987